Potential Overtreatment of Hyperglycemia in Older Adults: A Factorial Vignette Study of Primary Care Clinicians

A Dissertation
SUBMITTED TO THE FACULTY OF
UNIVERSITY OF MINNESOTA
BY

Ellen M McCreedy

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Robert Kane, MD

July, 2016

1 Acknowledgements

Thank you to my advisor, Dr. Bob Kane, who challenged me to grow academically and personally during my time at the University of Minnesota. I am proud to have been mentored by someone who will never give up trying to change the world, one student at a time.

Thank you to Dr. Rosalie Kane for our long car rides. I learned so much from you, about life, family, and treating every person with the dignity and respect she deserves.

Thank you to Dr. Mary Butler who leads by example. It was a gift to work for someone who is as exceptionally intelligent as she is intuitive. You were a reflection for me of what was possible. I am forever grateful for your influence on my path.

Thank you to all the professors that I have worked for or have become close to during my time at the University, especially: Dr. Donna McAlpine, Dr. John Nyman, Dr. Bryan Dowd, and Dr. Todd Rockwood.

Thank you to my committee members: Dr. Sarah Gollust, Dr. Kirby Clark, and Dr. Nathan Shippee. You stuck with me through the ups and downs of data collection, focusing on the process and the experience of completing a dissertation – lessons I hope to share with my students one day.

Thank you to the support staff who really are the lifeblood of this program. Ms. Maureen Andrew, thank you for providing that extra encouragement and a safe place to vent. Thank you to Ms. Sarah Trachet who keeps us in-line, but also has a huge heart. Thank you to the Center on Aging staff (past and present): Ms. Marilyn Eels, Ms. Nancy Russell, and Ms. Cheryl Cole-Hill.

Thank you to my family. Thank you to my aunts, Kit and Ginny, and my cousins, Sophie and Sanjana, for opening up their home and their hearts to me for the past six years. You are the best part of Minnesota, and I hope you continue to be in my life. Thank you to my Florida family, particularly Moe and Peg, for your continued support and love. Thank you to my family of origin, especially my Mom who passed her love of learning and compassion onto me.

Thank you to my cohort members. We are an awesome cohort and I will miss each of you in too many ways to mention. Thank you, Dongjuan, for being my true-blue friend, in good and hard times. Thank you, Sirry, for the laughs, cries, drinks, and continued love.

Thank you to the Florida Ladies, especially Ligia. I am grateful to be part of such an inspiring, trail-blazing group of women.

Thank you to RT and JR for believing in me and giving me the tools to believe in myself.

2 Dedication

This dissertation is dedicated to my partner whose self-respect, discipline, and unconditional love continue to make me a better person.

3 Abstract

Background

Diabetes is characterized by high blood sugar, or hyperglycemia. In addition to diet and exercise, several classes of medications are commonly used to treat hyperglycemia in type 2 diabetes in an attempt to reduce the downstream micro- and macrovascular complications of the disease. Four large trials showed few benefits and significant harms from attempting to achieve near normal glycemic control in middle aged people with type 2 diabetes. Benefits of aggressive glycemic control are further reduced for older adults with longstanding disease, those who have accumulated many of the complications of diabetes, and people with other comorbid conditions that limit life expectancy. This more complex older adult population is also at greater risk of iatrogenic hypoglycemia, a harm associated with treatment. For these reasons the American Diabetes Association and the American Geriatric Society have published guidelines recommending less stringent glycemic control for older adults with multiple comorbid conditions and limited life expectancies. However, little is known about how these guidelines are being implemented by primary care clinicians who provide most of the chronic disease management in the US.

Methods

A factorial vignette study was used to determine the effect of the patient characteristics mentioned in the existing guidelines on a clinician's decision to prescribe a second-line treatment to achieve tighter glycemic control. The factors varied were patient age / disease duration (65 with short disease duration, 80 with long disease duration), cardiovascular disease (no heart disease, coronary artery disease with previous bypass), and cognitive impairment (no impairment, cognitive impairment that restricted ability to drive). Two policy-relevant glycated hemoglobin (HbA1c) levels were varied in the vignettes: 7.5% or 8.5%. Independent and combined effects of patient factors (patient complexity) were considered. Primary care clinicians from around the US were asked to participate via email. Clinician information was collected, including: years in practice, familiarity with treating older adults, and clinician type (family, internal, nurse

practitioner). Clinicians were also asked to predict how likely the hypothetical patient was to adhere to their medication choices. Mixed effect models were used to account for the panel nature of the data (clinicians viewing multiple vignettes).

Results

366 primary care clinicians from 36 states participated, with the majority of respondents practicing in Minnesota (35% of sample) or Florida (26% of sample). While we found some sensitivity to the patient factors mentioned in the existing guidelines, we also found evidence of overtreatment of the most complex hypothetical patients. For example, an 80-year-old with longstanding diabetes, cognitive impairment, and coronary artery disease requiring bypass had a second-line treatment added 35% of the time at a HbA1c level of 7.5%, and 75% of the time at a HbA1c of 8.5%. The same patient was recommended a sulfonylurea or insulin (agents known to increase the risk of iatrogenic hypoglycemia) 36% of the time at a HbA1c level of 7.5% and 44% of the time at a HbA1c level of 8.5%. Family practice physicians were less likely to add an additional medication than internal medicine physicians or nurse practitioners. Clinicians did not incorporate their adherence predictions into their decisions to intensify medication therapy.

Conclusions

This work is part of a larger discussion around balancing the risks and benefits of aggressively treating hyperglycemia in older adults with type 2 diabetes for whom tight glycemic control produces few benefits and significantly increases risk for iatrogenic hypoglycemia. Clinicians may treat more aggressively than guidelines recommend because they are unfamiliar with the geriatric-specific guidelines or they may work in settings where performance incentives are tied to achieving HbA1c levels recommended for average or healthier patients. As few benefits and serious harms are associated with overtreatment, policy recommendations include: 1. creating performance incentives to reduce anti-glycemic medication therapy when appropriate; and 2. developing tools to help primary care clinicians evaluate complexity and life expectancy in their older patients with multiple chronic conditions.

Table of Contents

4 List of Tables

5 List of Figures

6 Introduction

Chronic disease accumulates with age and is a central issue in geriatric care. Approximately one in three people in the United States will develop diabetes, at some point in their lives.[1] In 2012, the CDC estimated there were 21.0 million people with diagnosed diabetes and 8.1 million people with undiagnosed diabetes living in the United States, or 9.3 percent of total population; 11.2 million of these diagnosed and undiagnosed diabetic cases were over 65 years of age.[2] Improved therapeutic remedies are allowing more people who are diagnosed with type 2 diabetes in middle age to live into older adulthood.[3]

For otherwise healthy adults with diabetes, physicians prescribe medications to achieve near-normal glycemic control and slow the downstream vascular complications associated with prolonged hyperglycemia. However, for older adults with longstanding diabetes, cognitive impairment, or cardiovascular complications, tight glycemic control can often come at the cost of increased risk of severe iatrogenic hypoglycemia.[4, 5] In fact, hospitalization rates for hypoglycemia now exceed those for hyperglycemia in the Medicare population and the rates of hospitalization for hypoglycemia double for patients with diabetes aged 75 or older compared to patients aged 65 to 74.[6] Finding a glycemic control "sweet spot" in older patients is complicated and a topic of debate.

Given the risk of severe hypoglycemia with tight glycemic control, the American Diabetes Association (ADA) and the American Geriatrics Society (AGS) recommend less stringent glycated hemoglobin (HbA1c) targets for older adults with diabetes who have limited life expectancy, cognitive impairment, longstanding disease, advanced microvascular or macrovascular complications, or multiple comorbidities.[7, 8] In general, these guidelines ask clinicians to individualize glycemic targets for medically complex, older adults to simultaneously avoid the risk of severe hypoglycemia while minimizing the effects of persistent hyperglycemia, such as cognitive dysfunction, dehydration or frequent urination.[7, 9] Existing recommendations also advocate for patient-centered glycemic targets that consider patient costs of care, patient motivation and ability to self-

manage, and the availability of resources of a support system.[10] We know very little about how providers apply these recommendations in practice.[11]

Most of the care received by older adult diabetics is provided by primary care providers,[12] the vast majority of whom are generalists, not geriatricians.[13] Only 23 percent of medical schools require a course in geriatrics and two-thirds of internists do not believe they are adequately trained in chronic care.[14] Primary care clinicians routinely choose between the 30 different medications from 9 unique drug classes approved for hyperglycemic management.[15] Complex decisions that occur in natural settings rely on established patterns, or heuristics, in which some information is consciously or unconsciously ignored by the decision maker.[16] Claims data and information from electronic medical records cannot help us understand underlying decision making processes. The use of factorial survey methodology is not new, but it has regained interest in recent years as a tool for unraveling complex medical decisions.[17-21]

Results of this factorial vignette study are presented as three short papers. The aims of the papers are to determine the independent and combined effects of patient HbA1c level, age, and presence of cognitive impairment and coronary artery disease on primary care clinicians':

Paper 1. Decisions to intensify first-line medication therapy (Figure 1, Model 1)

Paper 2. Choices between existing second-line therapies (when clinicians choose to intensify first-line treatment) (Figure 1, Model 1)

Paper 3. Adherence predictions (Figure 1, Model 2)

Papers 1 and 2 considered two ways clinicians can decrease the risk of serious iatrogenic hypoglycemia in older, more complex patients, either by not intensifying anti-glycemic medication therapy or by choosing a medication with a lower hypoglycemic risk profile. In Paper 3, we asked how a clinician's adherence prediction for a hypothetical patient with cognitive impairment affects her decision to intensify medication therapy. In all three papers, we also evaluate whether the clinicians' decisions vary by provider type, years of practice, length of routine visit, and familiarity with the Medicare population.

This work is part of a larger discussion around balancing the risks and benefits of aggressively treating hyperglycemia in older adults with type 2 diabetes for whom tight glycemic control produces few benefits and significantly increases risk for severe iatrogenic hypoglycemia. Clinicians have long known that hypoglycemia was a potentially severe side effect of antidiabetic treatment. However, the magnitude of this harm, particularly for older adults, has gained attention in the professional press[5, 22-25] and coincides with a growing societal discussion about how we can live meaningful, less medicated older lives.[26, 27]

7 Background

7.1 Diabetes in Older Adults

Diabetes is a group of metabolic diseases characterized by hyperglycemia, or high blood glucose, resulting from defects in insulin secretion, insulin action, or both. The two major classifications in use today, diabetes mellitus type 1 and diabetes mellitus type 2, were proposed by the National Diabetes Data Group in 1979 and confirmed by the World Health Organization in 1985.[28, 29] Type 1 diabetes, formerly insulin dependent diabetes, accounts for only 5-10 percent of all diabetes cases; it typically results in absolute insulin deficiency due to the autoimmune destruction of B-cells of the pancreas.[30] Type 2 diabetes, formerly non-insulin dependent diabetes, accounts for 90-95 percent of all cases and is characterized by insulin resistance with relative, rather than absolute, insulin deficiency.[30]

This vignette study focused on a case with type 2 diabetes of middle-age onset, distinguished by the duration of disease which indicates an onset around age 60, and an elevated body mass index (BMI). We chose to focus on middle-age onset because the four large trials that define what we know about the effect of tight glycemic control on outcomes in type 2 diabetes enrolled people with middle-age onset type.[9, 31, 32]

7.2 Goals of Anti-Hyperglycemic Medication Therapy

The hallmark of diabetes is elevated blood sugar levels, or hyperglycemia. In addition to diet and exercise, there is one widely accepted first-line medication (Metformin) for type 2 diabetes and six classes of second-line medications available to help reduce blood sugar levels in people with diabetes.[33] Diabetes causes significant morbidity and is a strong predictor of functional decline in older adults.[34-36] Treatment in diabetes is focused on slowing the development of microvascular and macrovascular complications associated with high blood sugar, or hyperglycemia, while avoiding harms related to significant lows in blood sugar, or hypoglycemia. The term iatrogenic hypoglycemia is used to refer to hypoglycemia resulting from treatment.

The current study considered a clinician's decision to intensify anti-hyperglycemic medication therapy by adding a second-line medication. In this section, we review the harms associated with prolonged hyperglycemia, or high blood sugar, that clinicians who intensify anti-hyperglycemic therapy are likely attempting to delay or prevent.

7.2.1 Microvascular Complications

The microvascular complications of diabetes include nephropathy (kidney damage), neuropathy (nerve damage), and retinopathy (retinal damage). Chronic sensorimotor neuropathy, (often characterized by patients as a tingling, pins-and-needles pain or numbness in extremities), is the most common microvascular complication in diabetes, occurring in over half of people with long-standing diabetes.[37] Careful monitoring and early treatment of neuropathic complications, including foot ulcerations, may help avoid late sequelae, including potential amputation.[37-39] Unfortunately, the reduced mobility and visual impairment of older subjects hampers their ability to inspect their feet, which is a fundamental component of diabetic foot care.[40, 41] Once foot abnormality is established, it leads to significant morbidity and mortality, which is accentuated in elderly diabetic patients. Compared to elderly people without diabetes, people with diabetes are 1.5 times more likely to have poor eyesight or blindness.[42] Approximately 40 percent of people with longstanding diabetes develop diabetic retinopathy.[42] Diabetic kidney

disease, or nephropathy, occurs in 20 to 40 percent of patients with diabetes.[43, 44] Twenty percent of those with nephropathic symptoms develop end stage renal disease (ESRD).[43]

Serious microvascular complications take a long time to develop. Aggressive glycemic control over an extended period (at least eight years) may slow the development of microvascular complications. Tighter glycemic control is more important for younger, otherwise healthier people with diabetes than for older people with diabetes and other conditions that limit their time to reap microvascular benefits of tight control.

7.2.2 Macrovascular complications

Macrovascular complications, including cardiovascular disease, stroke, and ultimately heart failure, are thought to be the result of narrowing of arterial walls, or atherosclerosis.[45, 46] Diabetes is often accompanied by obesity, hypertension, and high cholesterol, all of which increase the risk of macrovascular complications.[45] Patients with diabetes have an increased risk of cardiovascular disease, and are 1.5 to 4 times more likely to have a stroke than people without diabetes.[45, 47] However, once cardiovascular complications are established, tight glycemic control may confer additional risk of cardiac death for people with longstanding type 2 disease with low coronary artery calcium scores.[48]

Although researchers continue to look for the link between tight glycemic control and cardiac complications,[49, 50] the large trials did not find this link, at least for the first ten years.[32, 51, 52] In our vignette study, hypothetical patients either had no history of heart disease or had coronary artery disease that required a coronary artery bypass graft (CABG) one year ago. We expected clinicians to be more likely to intensify treatment for otherwise healthy people with diabetes and no history of heart disease to reduce downstream microvascular complications and, potentially, macrovascular complications, if the patient lives more than ten years.[22]

7.3 The Trials

Four large trials are the frequently cited evidence base for treating hyperglycemia in type 2 diabetes. It is important to review these trials in the context of the current work to understand the evidence on which the current guidelines were formed and the applicability of this evidence to specific subpopulations. Of interest in the current study, we sought to understand how the trial data applied to older adults with cognitive impairment and preexisting cardiovascular disease.

7.3.1 United Kingdom Prospective Diabetes Study (UKPDS) Trial

Between 1977 and 1991, the United Kingdom Prospective Diabetes Study (UKPDS) trial enrolled 5,102 newly diagnosed type 2 diabetics and, after three months of a dietary intervention, non-overweight volunteers were randomized to one of three study arms: diet only control, intensive treatment with sulfonylureas, or intensive treatment with insulin.[53] This trial excluded those aged 65 or older at baseline.[9] HbA1c target for the intensive treatment arms was below 7%; the diet only arm was provided medications only if HbA1c levels were well above 9%.[53] Overweight patients were randomized to one of four arms: diet only control; intensive treatment with sulfonylureas; intensive treatment with insulin; or intensive treatment with metformin.[53] Volunteers with any of the following characteristics were excluded: a myocardial infarction (MI) within the last year; heart failure; retinopathy requiring treatment; malignant hypertension; an occupation that prohibits insulin use; a life-limiting illness; or an "inadequate understanding" of how to manage their diabetes.[53]

After ten years, the average blood glucose in the diet only arm was 7.9% versus 7.0% in the intervention arms (medications combined).[53] At ten years, there were no significant differences in diabetes-related or all-cause mortality between diet only and medication arms.[53] Compared to diet alone, any medication decreased the likelihood of microvascular complications, primarily retinal photocoagulation; no differences in macrovascular complications were found.[53] Hypoglycemic episodes were significantly greater in the medication treatment arms.[53] The findings from the UKPDS trial, published

in 1998, focused national attention on the relative value of intensive blood pressure control over blood glucose control to affect morbidity and mortality in type 2 diabetes.[54]

The UKPDS trial was groundbreaking in its inability to show an association between glycemic control and macrovascular complications or death[53] However, relevant to the current study, the UKPDS looked only at people with newly diagnosed diabetes who were less than 65 years old with no serious complications or illnesses. Given that 45 percent of men over the age of 65 and 47 percent of women over the age of 65 have 2 or 3 chronic diseases,[55] the applicability of these results to a "typical" older adult with diabetes is relatively limited. This weakness was immediately recognized. Following the UKPDS, three large trials were conducted almost concurrently to consider the effect of intensive versus standard glycemic control on people with type 2 diabetes and established macrovascular complications.[32, 51, 52]

7.3.2 Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial

Beginning in 2003, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial enrolled middle-aged and older people (40-79, mean (±SD) of 62.2±6.8) with type 2 diabetes at high risk for cardiovascular events.[31, 51] Volunteers with the following histories were deemed not eligible: hypoglycemia, a previous cardiovascular event or procedure within the past three months, a medical condition that limits survival (<3 years), or factors likely to limit adherence.[31] The ACCORD trial compared cardiovascular events in volunteers with cardiovascular risk factors randomized to either near-normal glycemic control (HbA1c of <6%, 6.4% median achieved) or standard glycemic control (HbA1c between 7% and 7.9%, 7.5% median achieved).[51, 56] 10,251 volunteers from clinical research sites throughout the US and Canada were randomized to the near-normal or standard glycemic treatment arms.[51]

In 2008, about 3.5 years into the trial, the ACCORD investigators were forced to discontinue the near-normal arm of the trial after an increase in all-cause mortality, cardiovascular-related deaths, and nonfatal myocardial infarctions were reported.[51] The widely held belief that significant increases in hypoglycemic events in the near-normal

control arm are responsible for increased mortality has not been proven in post-hoc analyses.[57, 58] Composite measures of microvascular outcomes, including advanced nephropathy or diabetic eye complications, did not differ between the intensive and standard control arms; incidence of albuminuria was decreased in the intensive control arm.[59] The major contribution of the ACCORD trial was to caution providers against the goal of near normal glycemic control in patients with underlying cardiovascular risk factors.

7.3.3 Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Trial

Between June 2001 and March 2003, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial enrolled 11,140 volunteers with type 2 diabetes who were at least 55 years of age (mean (±SD) of 66±6) with a history of major macrovascular or microvascular disease with at least one other risk factor for vascular disease.[32] Similar to ACCORD, participants were randomized to intensive (HbA1c≤6.5% mean achieved) or standard glycemic control (target defined by local guidelines, 7.3% mean achieved) arms.[32] After 5 years of follow-up, intensive control reduced the incidence of any major microvascular event (largest contributor being new or worsening nephropathy), but did not impact the incidence of any major macrovascular event.[32] The ADVANCE trial did not find an increase in death in the intensively controlled arm.[32] Like the UKPDS and the ACCORD trials, the ADVANCE trial found intensive anti-glycemic treatment was associated with an increase in severe hypoglycemia.[32] The ADVANCE trial also reported an increase in hospitalization in the intensive treatment arm.[32]

7.3.4 Veterans Affairs Diabetes Trial (VADT)

Finally, between December, 2000 and May, 2003, the Veterans Affairs Diabetes Trial (VADT) enrolled 1,791 military veterans with inadequate responses to maximum doses of an oral agent or insulin therapy.[52] All participants had a HbA1c level >7.5%. (mean

(±SD) of 9.4±2 at baseline).[52] At baseline, 40% of participants had a previous cardiovascular event, 62% had a history of microvascular complications, and 52% were already receiving insulin.[52] The average age of participants was 60 at baseline (mean (±SD) of 60.3±9).[52] Intensive therapy involved maximum doses of oral agents followed by insulin for those who were not able to achieve HbA1c levels below 6% (6.9% mean achieved) on oral agents alone.[52] Participants in the standard therapy arms were administered half maximum doses, with insulin initiated only for those with HbA1c levels above 9% (8.4% mean achieved).[52] After 5 years, no significant difference in time to first cardiovascular event or cardiovascular-specific death was observed between arms.[52] All-cause mortality was not different between the two arms.[52] However, in the intensive control arm, there were significantly more sudden deaths and a significant increase in the number of more serious hypoglycemic events and other harms reported.[52] The only microvascular outcome that was positively affected by intensive control was progression of albuminuria; no significant differences in retinopathy, major nephropathy, or neuropathy were observed across arms.[52] Table 1 summarizes the outcomes of the ACCORD, ADVANCE, and VADT trials.

These three large trials launched a debate as to the relative benefits versus potential harms associated with tight glycemic control. The ADVANCE and VADT trials found aggressive glycemic control (<7%) in middle-aged people with diabetes and established macrovascular complications did not significantly reduce all-cause mortality, cardiovascular mortality, or macrovascular complications after five years. The ACCORD trial found an increase in all-cause mortality, cardiovascular-related deaths, and nonfatal myocardial infarctions after only 3.5 years.[51] Even the positive microvascular findings have been brought into question as differences in the intermediate outcome of albuminuria have not been significantly associated with differences in the patient-centered outcome of renal disease.[60]

However, the trials tell us virtually nothing about how to treat the older adult. Less than 0.5% of the ACCORD trial and 1.6% of the ADVANCE trial participants were 80 years old or older, and, starting in 2003, the ACCORD trial excluded patients over 80 due

to safety concerns related to tight glycemic control.[22] The existing trials highlighted the increased risk of hypoglycemia, particularly for older adults with longstanding disease,[48, 61] but did not provide guidance as to the optimal treatment targets for older adults with multiple conditions and limited life expectancy (who were largely excluded from participation). But, as is often the case in medicine, consensus guidelines have been developed to treat older adults with multiple chronic conditions, despite having very little or no evidence.

7.4 Guidelines for Setting Anti-hyperglycemic Treatment Targets

The relevance of this work to policy development depends on understanding existing recommendations for treating older people with diabetes. The American Diabetes Association's (ADA) "Standards of Medical Care in Diabetes" is a widely consumed position statement issued every five years, or as needed.[62] The ADA's position statement is peer reviewed and provides graded evidence for each clinical recommendation.[62] The most recent update of these standards was published in 2016.[7, 62-64] In general, the ADA's 2016 Standards of Medical Care in Diabetes recommend HbA1c targets of <6.5% to <7% for patients with a short disease duration and no history of severe hypoglycemia or cardiovascular disease (Grade A evidence for <7%, Grade C for more stringent control).[65] However, for older adults with diabetes who have limited life expectancy, cognitive impairment, longstanding disease, advanced microvascular or macrovascular complications, or multiple comorbidities, the ADA recommends less stringent targets, such as <8% (Grade B evidence).[65] The exact language from the ADA Standards (Figure 2) specifically recommends less stringent glycemic targets in older adults with decreased autonomic responses, which allows for more effective detection and treatment of the early symptoms of hypoglycemia.[65]

In a separate chapter of the same guideline dedicated to the treatment of older adults, the standards provide more specific HbA1c targets based on cognitive and physical functioning, preexisting complications, and important comorbidity that limit life expectancy (Table 2).[7] The American Geriatrics Society (AGS) has since supported the

three-tiered, complexity-based targets in Table 2.[66] The AGS (2013) guideline recommends a blanket glycemic target of between 7.5% and 8% for older adults, with glycemic targets between 7% and 7.5% appropriate for otherwise healthy older adults, and glycemic targets between 8% and 9% for older adults with multiple comorbid conditions, poor functioning, and limited life expectancy.[8]

The current study considers how patient characteristics, mentioned in existing patient-centered guidelines, affect primary care clinicians' decisions to accept a certain HbA1 level or to intensify treatment.

7.5 KQ1 Relationship between Patient Vignette Characteristics and Treatment Intensification

We hypothesize glycated hemoglobin levels (HbA1c) levels, age/disease duration, cognitive impairment, and coronary artery disease to be related to a clinician's decision to intensify treatment in the following ways.

HbA1c

For this study, we systematically vary two HbA1c levels (7.5% or 8.5%) in the hypothetical patient vignettes. Based on the ADA guidelines[65] and many quality-based incentive payments tied to achieving HbA1c levels below 8% for all patients, we expect more treatment intensification at HbA1c levels of 8.5%.

Age

Increasing age is associated with a decrease in recommended treatment intensification, after controlling for a host of patient and provider factors, including comorbidities, level of patient adherence, and number of primary care visits.[67] Increasing age may be independently associated with non-intensification for the following reasons:

Hypoglycemia Decreased glucose counter-regulation [68-71] results in fewer warning signs of hypoglycemia and an increased risk of severe or even fatal hypoglycemia as people age.[9, 68] The UKPDS, ACCORD, ADVANCE, and VADT trials heightened awareness of hypoglycemic risks associated with tight control for

participants of all ages.[32, 51-54] Post-hoc analyses showed the risk of severe hypoglycemic events increases with age.[72, 73]

Life Expectancy Current guidelines suggest less intensive treatment for patients with limited life expectancy, as it takes approximately eight to ten years to realize the benefits of glycemic control.[63, 65, 74] Primary care clinicians experience uncertainty estimating and applying prognosis information into clinical decision-making.[75] Based on life expectancy tables developed from the UKPDS trial, the estimated life expectancy of a 55 year-old man who has had type 2 diabetes for five years is between 13.2 years and 21.1 years (variation described only by baseline HDL level and smoking status).[76] However, we know that life expectancy in older adults is quite variable, depending on important comorbidities, functional status, and cognition.[77, 78] Prognosis support tools, such as ePrognosis,[79] are being developed, but clinical judgement is most frequently used and largely inaccurate.[75, 80, 81]

Disease Duration For people with type 2 diabetes of middle age onset, as age increases, duration of diabetes increases. Longer duration of diabetes is associated with more established complications and an increased likelihood of adverse events (including hypoglycemia) from aggressive anti-glycemic treatment.[5] In the VADT, longstanding disease was associated with an increase in deaths in the intensive control arm.[9]

Polypharmacy Advances in medicine help people live longer, but with multiple co-morbid conditions and extensive polypharmacy.[82, 83] Evidence suggests the first anti-glycemic medication gives you the most "bang for your buck" and secondary treatments, meant to achieve tighter control, may results in increased adverse events (including unplanned hospitalizations) and drug-drug interactions.[22, 84, 85] PCPs may accept a higher HbA1c level or reduce/discontinue a current anti-hyperglycemic medication as patients age to avoid these harms. Currently rates of appropriate de-intensification are low.[86]

This study systematically varies two levels of patient age and disease duration in the vignettes: 65 years old with newly diagnosed diabetes, and 80 years old with longstanding disease. We expect clinicians to be less likely to intensify treatment for the 80-year-old patient with longstanding disease.

Cognitive Impairment

The decision to intensify anti-glycemic medication therapy for a person with cognitive impairment is complicated by multi-directionality in the blood glucose-cognition relationship. People with type 2 diabetes and cognitive impairment are more likely to have severe hypoglycemic events (potentially through the impaired self-management pathway explored in this study).[4] However, people with diabetes and a history of prior hypoglycemic events are also at greater risk for cognitive decline and dementia than those without a history of hypoglycemic events.[87, 88] Further, chronic high blood glucose, or hyperglycemia, also causes problems with cognition.[89] The current recommendations do not support intensive control to improve cognition.[7, 65] We expect for younger patients with short disease duration, few micro- and macrovascular complications or comorbid conditions, and evidence of cognitive impairment, clinicians may more aggressively treat hyperglycemia (particularly at 8.5%) than older patients with evidence of cognitive impairment and other comorbid conditions that limit life expectancy.

Coronary Artery Disease with Coronary Artery Bypass Grafting (CABG)

Although researchers continue to look for the link between tight glycemic control and cardiac complications,[49, 50] the large trials did not find this link.[32, 51, 52] On the contrary the ACCORD trial found an increase in cardiac-related deaths in the intensive treatment arm.[51, 90] Post-hoc analyses of the ACCORD and VADT suggested that tight glycemic control may confer additional risk of cardiac death for people with preexisting cardiovascular risk with longstanding type 2 disease who had low coronary artery calcium scores at baseline.[48] One explanation for this observed relationship is through the pathway of repeated hypoglycemic events, which we know are increased with tight

glycemic control. Hypoglycemic events stress the heart.[90] This stress may be unremarkable in otherwise healthy patients, but, in patients with coronary artery disease, the stress of a severe hypoglycemic event may result in acute vascular events or sudden death.[90] The relationship between hypoglycemia and cardiovascular deaths is also complex and debated.[48] In our vignette study, hypothetical patients either have no history of heart disease or have coronary artery disease that required CABG one year ago. We expect clinicians to be more likely to intensify treatment for the patient with no history of heart disease. This relationship may be modified by disease duration.

7.6 KQ2 Relationship between Patient Vignette Characteristics and Anti-glycemic Medication Choice

The case vignettes depicted hypothetical patients with elevated blood sugar levels (HbA1c levels of 7.5% or 8.5%) after three months of first-line Metformin treatment of 1,000 mg, twice a day. As discussed in KQ1, older patients with long-standing disease, cognitive impairment, or cardiac complications reap fewer benefits and are at greater risk for adverse events from tight glycemic control. A clinician considering these risks may decide not to add a second-line therapy or intensify treatment (focus of KQ1) or she may decide to add an additional agent with a lower risk profile (KQ2).

Metformin, a biguanide, is the widely accepted first-line treatment for hyperglycemia in type 2 diabetes, primarily because it does not cause weight gain, carries no risk of hypoglycemia, and it is inexpensive.[47, 91] Metformin primarily works by decreasing the amount of glucose produced by the liver, increasing insulin sensitivity. The main side effects of Metformin are gastrointestinal.[47]

If blood glucose, or HbA1c, targets are not met with one medication, current guidelines suggest adding an additional medication.[33] There are 11 classes of second-line medication anti-glycemic therapies currently approved for use (some approved only as adjunct therapies).

This study considered the 5 most common combination (second-line) therapies:

1. **Metformin** (Glucophage) + **Sulfonylurea** (Glipizide, Glyburide, Amaryl)
2. **Metformin** (Glucophage) + **Thiazolidinedione** (Pioglitazone, Actos)
3. **Metformin** (Glucophage) + **DPP-4 Inhibitor** (Januvia, Onglyza)
4. **Metformin** (Glucophage) + **GLP-1 Receptor Agonist** (Exentide, Liraglutide)
5. **Metformin** (Glucophage) + **Long-Acting Insulin** (Lantus, Glargine, Detemir, Levemir)

Sodium–glucose cotransporter 2 (SGLT2) inhibitors were not in widespread use when this study was designed and, therefore, is not offered as a second-line treatment option.

Second-line therapies are relatively similar in their effectiveness at reducing HbA1c levels.[47] However, important to this study, combination therapies differ in their hypoglycemic risk profiles. Compared to other combination therapies, people taking Metformin in combination with either a second-generation sulfonylurea or long-acting insulin are at greater risk of hypoglycemic events. People taking Metformin and a sulfonylurea are almost 6 times more likely to have a mild to moderate hypoglycemic event than those taking Metformin and thiazolidinedione, pooled OR of 5.8 (95% CI 4.3 to 7.7).[47] People taking Metformin and a sulfonylurea were 33% more likely to have a hypoglycemic event compared to those taking Metformin and DPP-4.[92] People taking Metformin and a sulfonylurea had 5 times as many hypoglycemic events as those taking Metformin and GLP-1 receptor agonists (5.32 versus .29 episodes per year).[93] Insulin has the highest rate of severe iatrogenic events of all therapies for type 2 diabetes.[33] Although sulfonylureas and insulins increase the risk of hypoglycemic events, they are the oldest and cheapest options for treating hyperglycemia (Table 3). The hypothetical patient in this study is able to afford her medications.

A priori, we expect clinicians who choose to intensify medication therapy by adding an additional medication to be more likely to choose second-line therapies with lower hypoglycemic risks and few side-effects (DPP-4 or GLP-1) for older patients with longstanding disease, cognitive impairment and coronary artery disease. Thiazolidinedione may increase the risk of congestive heart failure.[47] We expect

clinicians will avoid this medication, particularly for hypothetical patients with coronary artery disease.

7.7 KQ3 Relationship between Patient Vignette Characteristics and Clinician Predicted Adherence

Existing guidelines support the use of patient expected effort in determining appropriate glycemic targets, encouraging PCPs to provide less stringent HgA1c control to "less motivated, non-adherent" patients.[10] Approximately 30 percent of diabetics are non-adherent to diabetic medications.[94] Presence of cognitive impairment, particularly affecting executive and working memory, is a significant barrier to medication adherence in older adults.[95, 96] Poor adherence may lead to harms, including hypoglycemic events, if a person administers an incorrect or additional dose of an anti-hyperglycemic agent, particularly insulin.[24]

For that reason, clinicians should not intensify treatment when they believe a patient will have difficulty adhering to medications.[97] Existing guidelines support the use of patient expected effort in determining appropriate glycemic targets, encouraging PCPs to provide less stringent HgA1c control to "less motivated, non-adherent" patients.[10]

However, adherence information is not regularly available or obtained in practice. A study of audiotaped clinic visits found adherence was mentioned by either the physician or the patient for 62 percent of prescribed medications.[98] Forty percent of adherence discussions were initiated by the patients and most of the physician initiated inquiries consisted of simply asking the patient whether she takes her medications.[98] For the remaining 38 percent of medication decisions, adherence information is either not incorporated or influenced by provider adherence beliefs or predictions. This study is among the first to quantify the partially mediating role of physician adherence beliefs in treatment intensification for diabetics with hyperglycemia.

A priori, we expect clinicians to predict worse adherence for hypothetical patients with cognitive impairment. We do not expect being older or having coronary artery disease to affect adherence beliefs. People with diabetes and an additional comorbid

condition have better adherence than those with diabetes alone,[99] and patients under 60 years old had poorer adherence than their older counterparts.[100]

7.8 Provider Factors

A cohort study of federal employees with managed care in Maryland did not find correlation between provider factors (physician specialty, year of graduation from medical school, and physician gender) and the decision to intensify therapy ($p>.05$ for all factors).[101] This study is consistent with a HealthPartners Medical Group study in which physician age, gender, specialty, and size of diabetes panel did not predict variation in HbA1c levels.[102] Based on these studies, we do not have any reason to think that provider specialty (internal medicine, family practice, or nurse practitioner), length of routine appointment, or years in practice will influence the decision to intensify medication therapy, but we will examine differences by these commonly assessed variables.

The current study also considers the approximate percent of a clinician's practice that is Medicare (<25%, 25%-74%, ≥75%). We expect clinicians who report serving a higher percentage of Medicare patients will be more familiar with geriatric-specific recommendations for setting more lenient targets based on complexity and choosing medication that reduce hypoglycemic risk.[63] Clinicians who serve a greater percentage of older patients may also have developed more sophisticated algorithms to assess likely adherence.

The survey design, with clinicians viewing multiple vignettes, allows us to look at persistent choices and cluster effects. An example of a persistent choice is a clinician respondent that chooses the same medication choice for all four vignettes. Cluster effects are described using the intra-class correlation coefficient (ICC). The ICC describes the proportion of the total variance in an outcome (e.g. decision to intensify treatment) that is attributable to individual respondent characteristics.

8 The Survey

8.1 Designing Factorial Vignettes

This study used factorial survey methodology to analyze physician decision making. The aim of vignettes is to make explicit or standardize the information respondents use to come to a decision. Survey respondents are presented a systematically constructed scenario, or vignette, and asked to rate the vignette on a pre-specified dimension. In this case, respondents will be asked what anti-hyperglycemic treatment option they are most likely to recommend (Aim1 and Aim 2), and how adherent the patient is likely to be to the recommended treatment (Aim 3).

The patient factors varied in this study were chosen because they correspond with the ADA's recommendations for older adults with type 2 diabetes.[63, 65] The following patient factors were used to construct the vignettes (dimension levels provided in brackets): HbA1c (7.5%, 8.5%); age/disease duration (65 year-old with diabetes for 5 years, 80 year-old with diabetes for 15 years); cognitive impairment (no information, some recent memory loss on formal testing/depends on daughter to pay bills/stopped driving because she got lost); heart disease (no history of cardiovascular disease, coronary disease with coronary bypass 5 years ago). Table 4 presents the vignette factors and levels. 16 unique vignettes exist in the factorial population: 2^4. The factors listed in Table 4 were systematically varied over a base vignette as follows:

> **Base Vignette**: Mrs. Brown is [AGE] years old and has had type 2 diabetes for [DISEASE DURATION]. Three months ago, Mrs. Brown was prescribed Metformin 1000 mg (BID), an ACE inhibitor to control comorbid hypertension, and a low-dose aspirin. Mrs. Brown currently has a HbA1c of [HbA1c], a BP of 140/80 mmHg, and a BMI of 29. Her basic metabolic profile is normal and GFR > 60. Mrs. Brown has [CARDIOVASCULAR HISTORY]. Mrs. Brown reports an intermittent pain in her feet, but has difficulty localizing it. There is no history of depression. [MEMORY LOSS] Mrs. Brown is able to afford her medications.

Base Vignette with Factors (Level 2): Mrs. Brown is 80 years old and has had type 2 diabetes for 15 years. Three months ago, Mrs. Brown was prescribed Metformin 1000 mg (BID), an ACE inhibitor to control comorbid hypertension, and a low-dose aspirin. Mrs. Brown has a HbA1c of 7.5%, a BP of 140/80 mmHg, and a BMI of 29. Her basic metabolic profile is normal and GFR > 60. Mrs. Brown has coronary artery disease, for which she underwent a coronary artery bypass graft five years ago. Mrs. Brown reports an intermittent pain in her feet, but has difficulty localizing it. There is no history of depression. Mrs. Brown has some recent memory loss on formal testing. She lives independently, but depends on her eldest daughter to keep her medical appointments and pay her bills. She stopped driving, in part because she occasionally got lost. Mrs. Brown is able to afford her medications.

Each respondent viewed four vignettes. The following surnames were used in the same order for each survey: Williams, Johnson, Jones, and Brown. These names were chosen because they are common surnames for black and white people in the United States. All hypothetical patients were female. In response to the vignette, providers were asked:

1. To choose the treatment option they are most likely to recommend (Continue Metformin monotherapy, Metformin and Sulfonylurea, Metformin and Thiazolidinedione (TZD), Metformin and a DPP-4 Inhibitor, Metformin and a GLP-1 Receptor Agonist, and Metformin and Long-Acting Insulin); and
2. To determine how adherent the patient is likely to be to her recommended medications (very unlikely to adhere, somewhat unlikely to adhere, somewhat likely to adhere, very likely to adhere)

Additional provider specific information was collected including year clinician finished professional education (year reported), specialty type (family medicine, internal medicine, nurse practitioner), average length of patient visit (reported in minutes), and percent of practice that is Medicare (<25%, 25%-74%, ≥75). At the end of the survey,

respondents were invited to provide information about how anti-hyperglycemic decisions were made in practice using an open text field.

8.2 Target Population, Sample Frame, and Sample Size

The target population was primary care clinicians who actively provide primary care at least 75% of the time. This is a non-probabilistic sample. In probabilistic sampling, a random sample is drawn from the entire population of interest. Probabilistic sampling, therefore, implies the population has been enumerated and each member of the population has equal probability of being selected for the study sample. In contrast, purposeful non-probabilistic sampling, as was used in the current study, has a population of interest (primary care clinicians), but participants are not randomly selected from that population.

This study used AHRQ's practice-based research networks and publicly attainable state licensure lists to obtain its sample. It is likely that the providers who participate in a voluntary research network, provide a working email at licensure, and reply to an unsolicited request to complete a survey are different from those who did not participate in some unobserved way. We expect physicians that participate may be more familiar with current guidelines or interested in research than those who did not. Therefore, we were are not able to generalize to the entire population of primary care physicians in the United States.

For each aim, we first conducted bivariate comparisons for categorical predictors using the chi-square test ($\chi 2$). The unit of analysis in factorial surveys is the vignette. 336 clinicians viewed four vignettes, resulting in 1,344 observations. With 1,344 observations, this study is 95% powered to find a 10% absolute difference between two groups [$\chi 2$ (1, N=1344)=3.84, p=.05].

However, these observations were not independent because each clinician respondent viewed more than four vignettes, leading to nested or hierarchical data. To estimate sample sizes for hierarchical models, we used simulation. For each aim, we:

1. Generated a data set with the appropriate number of predictor variables and variable groups
2. Generated the outcome variable(s), yij, based on what the literature suggested was the relative importance of each predictor for that outcome.
3. Made an assumption as to the total variation in the decision or prediction of interest that would be explained by our models. Taylor (2006) suggests that factorial surveys typically explain about 30 percent of the variance in decisions.[20] We chose a more conservative 20 percent.
4. Ran the regression models to determine whether or not we are powered to detect a significant difference (p=.05) in the marginal effects for each predictor variable. We then bootstrap the standard errors to ensure stable estimates.

From these simulation studies, we determined that with 1000 observations from 300 physician clusters, we are able to detect significant marginal effects for all proposed predictors and two-way interactions.

8.3 Data Collection and Survey Development

The final survey tool was developed after carefully incorporating clinician feedback from two pilots. The first, in-person pilot allowed the primary investigator to interact with respondents to gather real-time feedback on item wording, survey structure, and response barriers. However, the first pilot was conducted on a clinician leadership population who spent more time conducting research than the average primary care clinician. The second pilot incorporated some significant content revisions from the first pilot and targeted a more typical clinician population.

8.3.1 Pilots

Medical Association Meeting

In Fall 2013, this survey was piloted at the annual conference of the Minnesota Medical Association (MMA). Protocol for this study was submitted to the University of Minnesota IRB Human Subjects Committee. The committee determined that the study is

exempt from review under federal guidelines 45 CFR Part 46.101(b), study number 1305E33481. 112 physicians attended the conference; 37 of which were family medicine or internists (eligible for participants). Of the 37 eligible physicians, 30 (81%) completed a questionnaire (120 vignettes, 119 with non-missing information). The PI (EM) and two of her colleagues located themselves at a table within a central thoroughfare inside the conference hotel. Conference participants, identified by the presence of a name badge, were approached. The researcher introduced herself as a doctoral student from the University of Minnesota completing a study on diabetic anti-hyperglycemic medications. The potential respondent was asked if s/he is a practicing primary care physician. If the potential respondent was a practicing primary care clinician and was willing to complete a five minute survey, copies of the participant consent statement and the survey tool, along with the researcher's business card, were provided. The clinicians were asked to complete the three-page, single-sided survey using the pen and clipboard provided. The survey was printed using the University of Minnesota, School of Public Health letterhead to convey authority. Respondent names and organizations were not collected. Surveys were identified numerically.

The conference setting of our first pilot allowed us to conduct three formal "think-alouds," processes in which respondents verbalize their thoughts as they complete the survey. Through this process, we began to identify clinical issues that could frame ultimate results, including lack of familiarity or trust with newer medications. Physician respondent comments suggested older medications work well and cost less, and the newer drugs may be a "drug company thing." Also, we were questioned as to the use of Metformin with 80-year-old patients, with a few respondents believing that Metformin was contraindicated for elderly patients. This is, presumably, out of a fear of lactic acidosis. However, current evidence suggests the risk of Metformin-related lactic acidosis is quite small, particularly among older adults with adequate kidney function, and this risk pales in comparison to hypoglycemic risks.[91, 103-105]

Significant changes made to the survey as a result of the first pilot included:

1. Lowered HbA1c levels. In the first pilot, we used highly-elevated levels (8.5%, 9.3%, 10.1%). At these levels, 99.2% of the hypothetical vignettes had their treatment intensified. The final levels chosen were 7.5% and 8.5%.
2. Provided creatinine clearance (kidney functioning) information for the 80 year-old. In the final version of the survey, adequate glomerular filtration rate (GFR) was included in the static vignette information.

Large Health System

In September 2014, we began working with a large Midwest health system. Over the next four months, we worked with our internal champion and their research center to modify the survey to benefit both parties. Before administering the second pilot, we increased the dose of Metformin from 850 mg (BID) to 1000 mg (BID) and eliminated the option to increase Metformin. Physicians felt that increasing Metformin may not be considered treatment intensification, but, instead, finishing a course of treatment. In Spring 2015, we collected 35 surveys (140 observations) from practicing clinicians. Important observations from this pilot included:

1. We observed more variation in intensification at HbA1c of 7.5% than the values used in the previous pilot. However, intensification at 8.3% was 98%.
2. Almost 25% of 80-year-olds with cognitive impairment had their treatment intensified with a sulfonylurea or insulin.

8.3.2 Final Survey

The final survey, administered in Fall 2015, focused more specifically on the characteristics mentioned in the ADA guidelines for older adults. History of coronary artery disease was added to age and cognitive impairment in the final version of the survey. A sample of the final participant consent statement and survey instrument are provided as Appendix A.

To reach a larger audience, we created an electronic version of the survey using the survey software supported by the University of Minnesota, Qualtrics.[106] Qualtrics had several advantages over the paper and pencil administration method used in the pilot:

- The software was able to randomly select four vignettes from the universe of 16 vignettes for each survey;
- The survey could now be shared via a common link that can be embedded in an email or newsletter;
- Additional statistics were made available to the researchers including survey completion time and counts of incomplete surveys; and
- We were able to maintain anonymity of participants, while tracking group-level deliverables for participating organizations.

Using contact information publicly available from the AHRQ's practice-based research network (PBRN) registry (https://pbrn.ahrq.gov/pbrn-registry), we contacted over 40 networks that were comprised of practicing primary care clinicians. A sample approach email is provided as Appendix B. Six networks agreed to participate (2 national, 4 regional) and forwarded a standardized link with an embedded email to their membership (Appendix C). This approach had a low yield of 10-15 respondents per network.

To increase the number of respondents, we used state licensure lists. We downloaded the Florida nurse practitioner and physician licensure lists from the state website (https://appsmqa.doh.state.fl.us/downloadnet/GeneralInformation.aspx). There was no fee associated with accessing Florida licensure lists. The Minnesota physician licensure list was accessed for a fee ($120 for Excel spreadsheet with contact information). Emails were available for approximately 60% of licensed physicians and nurse practitioners. After cleaning for specialties of interest, we sent emails to over 10,000 recipients (Appendix C). Emails were sent in batches from the primary investigator's University email address with 500 blinded recipients per email (max allowed by Gmail). We were not able to easily send follow-ups using this method, as we received 'do not contact' responses from the first wave. We did not want to risk re-contacting those participants with a reminder email. The undeliverable rate was relatively low (between 5 and 7 percent); email addresses provided during licensure were mostly valid. However, there is no research on the percent of emails provided for licensure that are actively monitored.

Therefore, we do not know the true denominator for either AHRQ PBRNs or the licensure samples. The response rate for PBRNs may be as high as 15% to 20%; the response rate for licensure-based samples is less than 5 percent.

8.4 Sources of Survey Error & Limitations

Sampling Error

This is a non-probabilistic sample. Our sample frame is not representative of all primary care physicians. Licensure lists have less sampling error than PBRNs.

Measurement Error

Measurement error is the result of poorly worded survey items. Measurement error results in inaccurate or uninterruptable responses. This tool was designed as part of a survey design course and received expert review from a practicing primary care physician. The tool was also piloted twice and think-alouds were conducted. We feel we have anticipated many of the sources of measurement error in this survey.

Nonresponse Error

This is the largest threat to quality in this survey. Nonresponse error occurs when people who respond to the survey are different than those that do not respond. Clinicians who participate in PBRNs are different from those who do not participate. Clinicians who provide emails during licensure are different from those who do not; clinicians who respond to unsolicited emails to complete surveys without financial incentive are different than those who do not. We can only speculate on the direction of this bias. We hypothesize clinicians who participated are more likely to be interested in research and familiar with current guidelines than those who did not, biasing our results conservatively (less inappropriate intensification that actually exists if the full universe of clinicians were available).

Coverage Error

Coverage error occurs when every member of the population does not have an equal chance of being included in the sample. In our sample, coverage error may be related to PBRNs in certain areas of the country being less likely to participate and licensure email address information not being publicly available for most states.

Other Limitations

Vignettes provide a starting point for considering physician decision making. However, hypothetical vignettes are not able to capture all information obtained in a clinical encounter, and the subtleties of this information.[107] During the first, in-person pilot, a few clinician respondents mentioned that they have conversations to find ways to improve adherence in their patients, and they found it difficult to predict adherence without the context of those conversations provided in the vignettes. However, the evidence suggests these conversations do not routinely occur.[98] Vignette research, while not devoid of social desirability bias, is more effective for assessment of clinical decision- making than chart review.[108]

9 Analyses

Two different types of outcome variables were used in this study: dichotomous (decision to intensify, predicted adherence) and categorical (choice of anti-hyperglycemic medication combination). Bivariate comparisons for categorical predictors ($\chi 2$), as well as mixed effects probit regression (Aim 1, Aim 3) and multinomial regression models (Aim 2) were used to estimate the effects of patient and provider level information on the clinical decisions and the PCP's prediction of likely patient medication adherence.

We report marginal effects. The marginal effects in probit analysis are the percentage point increase or decrease in the probability of outcome (yij) given a one-unit change in a predictor variable. For example, being 80 years old, compared to 65 years old, is associated with a 5 percentage point decrease in the probability of treatment intensification. In multinomial probit, the percentage point increase or decrease in probability of outcome (yij) for any given category is referenced to a base category. In Aim 3, the reference category is continuing Metformin monotherapy.

We also used regression models to account for the panel nature of the data (clinicians viewing multiple vignettes). To accurately determine sample size, we simulated a data set and ran a macro to determine the stability of significant results. The percentage of the time significant betas are achieved on all independent variables is the power (e.g. 80%).

Because the estimates from the TRIAD studies were available for age and HbA1c, we chose to determine our sample size based on Aim 1, the decision to intensify treatment. The effect sizes suggested by the literature are a 5 percentage point decrease in intensification based on age (50-64 vs 75-85) and a 25 percentage point increase based on HbA1c (7-8% versus >8%).[67, 109, 110] We did not have literature to support effect sizes related to treatment intensification for cardiovascular disease or cognitive impairment. For these two factors, we chose a conservative 5 percentage points. A priori, we estimated that with 400 observations from 100 physician clusters, we are able to detect significant marginal effects for all four vignette-level variables and two provider-level factors. Our final sample included 1344 observations from 336 clinicians which allows us to look at all vignette and provider level factors and vignette-level interactions. To complete the simulation, we also needed to make an assumption as to the total variation in the decision or prediction of interest that could be explained by our models. Taylor (2006) suggests that factorial surveys typically explain about 30 percent of the variation in decisions.[20] We chose a more conservative 20% of variation. What follows are the equations that were used for each Aim.

Aim 1. Determine to what extent patient and provider factors affect a PCP's decision to intensify medication treatment.

Yij = B1(HgA1c)ij + B2(Age)ij + B3(Cogntive_Status)ij + B4(Cardiac_Complications)ij + B6(yrs_experience)j + B7(specialty_type)j + B8(average_appt_length)j + B9(%_Medicare)j + Uj + Eij

Where:

Y_{ij} = the likelihood of intensification for vignette i for clinician j;

x_{ij} = the value of the patient and provider characteristics for vignette i for clinician j, and

β_p = the regression coefficients that show how X variables affect choice

Aim 2. Determine to what extent patient and provider factors affect a PCP's choice of anti-hyperglycemic medication

Yij = B1(HgA1c)ij + B2(Age)ij + B3(Cogntive_Status)ij + B4(Cardiac_Complications)ij + B6(yrs_experience)j + B7(specialty_type)j + B8(average_appt_length)j + B9(%_Medicare)j + Uj + Eij

Where:

Y_{ij} = the choice of anti-hyperglycemic medication combination for vignette i for clinician j;

x_{ij} = the value of the patient and provider characteristics for vignette i for clinician j, and

β_p = the regression coefficients that show how X variables affect choice

Aim 3. Determine to what extent patient and provider factors affect a PCP's prediction of likely patient medication adherence.

Yij = B1(HgA1c)ij + B2(Age)ij + B3(Cogntive_Status)ij + B4(Cardiac_Complications)ij + B6(yrs_experience)j + B7(specialty_type)j + B8(average_appt_length)j + B9(%_Medicare)j + Uj + Eij

Where:

Y_{ij} = the prediction of patient adherence for vignette i for clinician j;

x_{ij} = the value of the patient and provider characteristics for vignette i for clinician j, and

β_p = the regression coefficients that show how X variables affect choice

Mediation

Using the results from Aim 1 and Aim 3, we determined to what degree provider adherence predictions partially mediate the relationship between cognitive impairment and the decision to intensify treatment (Figure 1, Model 2). For mediation to occur, four things must be true:

1. Cognitive impairment must be significantly associated with clinician predicted adherence;
2. Cognitive impairment must be significantly associated with intensification in the absence of predicted adherence;

3. Clinician predicted adherence must be significantly associated with intensification; and
4. The effect of cognitive impairment on intensification must become smaller in the presence of clinician predicted adherence.[111]

In addition to observation of coefficients, mediation was formally tested using Sobel-Goodman test.

10 Paper 1. Antidiabetic Treatment Intensification for Older Diabetics with Cognitive Impairment and Preexisting Heart Disease: A Factorial Vignette Study

Introduction

For otherwise healthy adults with diabetes, physicians prescribe medications to achieve near-normal glycemic control and slow the downstream microvascular complications associated with prolonged hyperglycemia. However, in older age, the therapeutic window narrows substantially. For older adults with longstanding diabetes, cognitive impairment, or cardiovascular complications, tight glycemic control can come at the cost of increased risk of iatrogenic hypoglycemia, without vascular benefit.[6, 112] In fact, hospitalization rates for hypoglycemia now exceed those for hyperglycemia in the Medicare population and the rates of hospitalization for hypoglycemia double for patients with diabetes aged 75 or older compared to patients aged 65 to 74.[6] Finding a glycemic control "sweet spot" to minimize both the risk of hyperglycemia and hypoglycemia in older patients is complicated and a topic of debate.

In general, the American Diabetes Association's (ADA's) 2016 Standards of Medical Care in Diabetes recommend glycated hemoglobin (HbA1c) targets of <6.5% or <7% for patients with a short disease duration and no history of severe hypoglycemia or cardiovascular disease.[65] However, for older adults with diabetes who have limited life expectancy, cognitive impairment, longstanding disease, advanced microvascular or macrovascular complications, or multiple comorbidities, the ADA recommends less stringent targets, such as <8%.[65] In a separate section of the same guideline, dedicated to the treatment of older adults, the ADA standards provide more specific HbA1c targets based on cognitive and physical functioning, preexisting complications, and important comorbidity that limit life expectancy (Table 1.1).[7] The American Geriatrics Society (AGS) supports the three-tiered, complexity-based targets in Table 1.1 with stricter lower thresholds,[66] recommending a blanket glycemic target of between 7.5% and 8% for older

adults, with glycemic targets between 7% and 7.5% appropriate for otherwise healthy older adults, and glycemic targets between 8% and 9% for older adults with multiple comorbid conditions, poor functioning, and limited life expectancy.[8]

It is not clear how familiar the average primary care clinician is with these geriatric-specific recommendations. Most of the care received by older adult diabetics is provided by primary care providers,[12] the vast majority of whom are generalists, not geriatricians.[13] Complex decisions that occur in natural settings rely on established patterns, or heuristics, in which some information is consciously or unconsciously ignored by the decision maker.[16] Little is known about how primary care clinicians incorporate the multiple patient characteristics mentioned in existing guidelines into their HbA1c treatment targets for older adults. The use of factorial survey methodology is a useful tool for unraveling complex medical decisions.[17-21, 113]

The objective of this research is to determine how patient characteristics associated with an increased risk of iatrogenic hypoglycemia, age/disease duration, cognitive impairment, and cardiovascular disease, affect a primary care clinician's decision to intensify treatment by adding a second-line medication. We designed a vignette study in which we systematically varied these patient factors at two policy-relevant HbA1c levels: 7.5% and 8.5%.

Methods

This study used factorial survey methodology to analyze clinician decision making. The aim of vignettes is to make explicit and standardize the information respondents use to come to a decision. Survey respondents were presented a systematically constructed scenario, or vignette, and asked to rate the vignette on a pre-specified dimension. In this case, respondents were asked whether or not they would intensify medication therapy in response to poor glycemic control after six months of first-line, Metformin therapy.

Vignette Design

Patient hemoglobin level, age/disease duration, presence of cognitive impairment, and history of coronary artery disease with a previous coronary artery bypass graft (CABG) were randomly varied in the vignettes. Each patient factor had two levels (Table 1.2),

yielding 16 possible vignette combinations. Patient gender, comorbid hypertension, body mass index, adequate glomerular filtration rate, mild neuropathic symptoms, lack of depression history, and medication affordability were held constant across vignettes. Five surnames that are common to both African Americans and White were used in an effort not to cue race. Each respondent viewed four, randomly selected vignettes. A sample vignette and the response set are provided (Figure 1.1). A priori, based on existing guidelines and recommendations, we expected clinicians to be most likely to intensify treatment for the 65-year-old, with a higher HbA1c, no cognitive impairment, and no history of cardiovascular disease.

Measures

Treatment intensification was defined as adding any one of five classes of approved second-line medication therapies. For the purposes of this analysis, a dichotomous variable was created to indicate intensification of medication therapy. Any choice other than continuing Metformin monotherapy was categorized as treatment intensification. Sodium glucose cotransporter (SGLT) inhibitors were not in widespread use at the time this survey was developed and piloted, and, therefore were not part of the choice set. In addition to the patient characteristics that were systematically varied in the vignettes, a few clinician characteristics were also collected, including: year respondent finished professional education, average length of a routine visit (minutes), and percent of practice that is Medicare (<25%, 25-75%, >75%). We expected clinicians who were educated more recently or whose practice was predominately Medicare patients to be more familiar with tailored recommendations for older adults and, therefore, less likely to intensify medication therapy for the older patient with cognitive impairment and cardiovascular disease. We also investigated the effect of clinician type (family medicine physicians, internal medicine physicians and nurse practitioners) and routine visit length on the decision to intensify medication therapy.

Data & Sample

Data were collected between August and December, 2015. The 366 respondents included attendees of a state-level professional association meeting (n=20), members of

AHRQ's practice-based research networks (n=83), and primary care physicians and nurse practitioners emailed using state licensure lists for Minnesota and Florida (n=261). To be eligible, physicians and nurse practitioners had to be actively practicing primary care medicine at least 75% of the time. While geriatricians and specialists offer important perspectives on medication management for diabetics, this study focused on generalists and excluded specialists. Respondents attending a state professional association meeting completed the vignette survey in-person. Respondents from the practice-based research networks and those directly contacted were invited to participate by email and completed the survey online. All responses were collected anonymously using Qualtrics software.

Analyses

The effect of vignette characteristics on the decision to intensify treatment was studied using bivariate and multivariate regression. Clinician variables were included in the regression models. Because clinicians viewed more than one vignette, we needed a regression model that would account for correlations between responses from the same clinician, so-called clinician cluster effects. The regression model chosen for this analysis was random effects probit. Vignette and clinician characteristics were entered into the model as fixed effects, with a random intercept for each physician. This model allowed us to consider the intra-class correlation, or the amount of total variation that is attributable to idiosyncratic clinician effects. One planned interaction model (differing effect of vignette characteristics by HbA1c) and one post-hoc interaction model (differing effect of vignette characteristics by clinician type) were also conducted. All analyses were conducted using Stata v.14.

Results

366 clinicians from 36 states participated; more than half of the respondents practiced in either Minnesota (35% of sample) or Florida (26% of sample). 30 surveys (8% of respondents) were excluded based on their self-reported specialty: not provided or "other" (n=11), geriatric or palliative care (n=9), endocrinology or nephrology (n=10). Respondent characteristics for the 108 family medicine physicians, 73 internal medicine

physicians, and 155 nurse practitioners who completed the survey are provided in Table 1.3.

Respondents completed their professional education between 1955 and 2015 (mean 1996). Internal medicine physicians had more years on average since finishing their education (mean=1986). Nurse practitioners had fewer years since completion of their professional education (mean=2008). The length of a routine visit among responding clinicians varied from 5 to 90 minutes, with an average visit of 23 minutes in length. Average length of a routine visit was similar across clinician types. Respondents estimated what percentage of their practices are Medicare patients: 28% reported less than 25%; 20% reported greater than 75%; with the majority of respondents (52%) reporting between 25% and 75% of their practice consisted of Medicare patients. Nurse practitioners were the most likely to report having over 75% of their patient population enrolled in Medicare, followed by internal medicine physicians and family medicine physicians.

Table 1.4 describes intensification by vignette characteristics at HbA1c levels of 7.5% and 8.5%. 1,344 vignettes are included in this analysis (336 respondents, each viewing four vignettes). The largest driver of anti-hyperglycemic treatment intensification was HbA1c, with 56% of vignettes intensified for a hypothetical patient with a HbA1c of 7.5% and 86% of vignettes intensified for a hypothetical patient with a HbA1c of 8.5%. As expected, treatment intensification was significantly more likely for the younger patient with shorter disease duration and the patient who did not have cognitive impairment. However, having coronary artery disease with previous CABG increased the likelihood of treatment intensification (compared to hypothetical patients with no history of heart disease).

We found similar effects of patient characteristics on the decision to intensify medication therapy using mixed effects probit regression (Table 1.5, Model 1). Holding other patient characteristics at mean values, having a higher HbA1c (8.5% versus 7.5%) increased the probability of treatment intensification by 32 percentage points. Being 80 years old decreased the probability of treatment intensification by 21 percentage points,

compared to being 65 years old. Having cognitive impairment decreased the probability of treatment intensification by 11 percentage points. Coronary artery disease with previous CABG was not significantly associated with the probability of intensification, after holding other patient variables at means.

Adding clinician characteristics to the model did not change the key findings (Table 1.5, Model 2). Compared to nurse practitioners and internal medicine physicians, family medicine physicians were significantly less likely to intensify medication therapy. A longer average visit length, a practice that is predominately experienced with Medicare patients or with a practitioner who has completed professional education within the last five years, did not significantly affect the decision to intensify treatment. However, the interclass correlation reveals that almost 60% of the variation in the decision to intensify medication therapy was due to idiosyncratic, unmeasured clinician characteristics, not the patient or clinician factors measured in this study.

We also ran two interaction models (Table 1.5, Models 3 & 4). First, as HbA1c has the largest effect on the decision to intensify medication therapy, we wanted to understand if the effect of HbA1c was constant or differed by patient characteristics. We found clinicians are more likely to accept a higher HbA1c for patients with cognitive impairment, but not for older patients or patients with coronary artery disease (Model 3). We also wanted to understand if family medicine physicians are less likely to intensify therapy for all patients or only for those patients with characteristics that may warrant less intensive treatment. We did not find differential intensification among family medicine physicians by specific patient characteristics (Model 4).

Using the coefficients from Table 1.5, Model 3, Figure 1.2 compares the predicted probability of treatment intensification, by provider type, for the least and most complex patient vignettes. We find an 80-year-old woman with a HbA1c level of 8.5%, coronary artery disease, a previous myocardial infarction, and a level of cognitive impairment that prohibits driving has mean predicted probability of treatment intensification of 82% (95% CI: 68%,96%) among nurse practitioners, 78% (95% CI: 67%,88%) among internal medicine physicians, and 63% (95% CI: 51%,75%) among family medicine physicians.

The same, medically complex woman with a HbA1c of 7.5% has mean predicted probability of intensification of 43% (95% CI: 35%, 51%) among nurse practitioners, 37% (95% CI: 27%, 47%) among internal medicine physicians, and 23% (95% CI: 16%, 30%) among family medicine physicians.

Discussion

Clinicians were sensitive to individual patient factors mentioned in existing treatment guidelines, but results suggest overtreatment relative to existing guidelines. Clinicians were less likely to intensify medication therapy for an older patient with a history of coronary artery disease and cognitive impairment, but intensification rates were still high for the most complex patients: 35% of most complex patients had treatment intensified at HbA1c of 7.5%, 75% at HbA1c of 8.5%. This is noteworthy because evidence suggests outcomes for older people with diabetes are likely optimized at HbA1c levels between 7.5% and 9.0%,[114] or between 8% and 9% for a nursing-home eligible population.[115] The risk of potential overtreatment of medically complex older people with diabetes varied by provider type. Family medicine physicians are less likely than internal medicine or nurse practitioners to intensify medication treatment. However, this difference in intensification patterns by specialty was not sensitive to individual patient characteristics, including HbA1c level, age/disease duration, coronary artery disease, or cognitive impairment. While this conservative behavior benefits the population of interest in this study (older adults with multiple comorbid conditions), potential under-treatment of younger, healthier patients was also observed and warrants further study.

This study has some limitations. The most common critique of factorial vignette studies is external validity and various forms of response bias. Research has demonstrated that physician behavior in response to vignettes is a valid way to measure quality, comparable to the gold standard of standardized patients, and better than relying on chart abstraction.[116] We also acknowledge that the clinicians who responded to this survey are different from those who did not respond in meaningful ways. However, if anything, we expect that clinicians who are part of practice-based research networks or who respond to an unsolicited invitation to participate in survey about diabetes care are

more likely to be familiar with existing guidelines than clinicians who did not respond. This would bias our results to be more conservative than if we were able to get a representative sample of all clinicians. This assumption seems to be substantiated by recent publications. Using HbA1c measures available in the National Health and Nutrition Examination Survey (NHANES), Lipska et al. (2015) found no significant differences in level of tight HbA1c control (<7%) between relatively healthy diabetics and older diabetics with complex or poor health (e.g. patients with end-stage renal disease, heart failure, or severe cognitive impairment).[117] Feil et al. (2011) found more intensive anti-glycemic management in older veterans with dementia than in those without cognitive impairment.[118] The magnitude of the potential overtreatment of hyperglycemia in this population is just beginning to be quantified, but likely exceeds 50% for older adults with multiple comorbid conditions (overtreatment variously defined as actively controlled to HbA1c levels <7% or 7.5%).[86, 113, 119-121] We estimate overtreatment, defined as treatment intensification for the most complex hypothetical patents with HbA1c levels of 7.5%, to be around 35%. It is likely clinicians who responded to this survey are more familiar with existing guidelines or research than the average clinician.

One policy option to address overtreatment may be to provide incentives for appropriate de-intensification[86] or lower rates of hypoglycemia.[122] Our findings suggest clinicians are much less comfortable with HbA1c values over 8%, even for patients who will not have time to benefit from the downstream macrovascular or microvascular complications associated with tighter control. Many primary care clinicians may work in settings where performance incentives are tied to achieving HbA1c levels under 8%, or even under 7%. Clinicians reported compliance with performance metrics as a barrier to implementing existing HbA1c recommendations for older adults.[113] Altering performance metrics to consider harms or patient safety may be have positive effects for the elderly, but unintended consequences of such policies, such as boosting the market for newer, pricier medication needs to be carefully monitored.[122]

However, clinicians may also be hesitant to allow for HbA1c levels between 8% and 9% because there is very little evidence to support these recommendations. Several large trials have illuminated short-term harms associated with attempting to achieve near-normal glycemic control (HbA1c of <6.5%) in older patients with cardiac complications,[32, 51, 52, 112] but no randomized controlled trials have considered the longer-term effects of managing patients to the less stringent HbA1c levels mentioned in the existing guidelines (7.5%-9%).[60, 74] Randomized controlled trials are needed to consider the longer-term effects of managing older, medically complex patients to current guideline recommendations.[60, 123] While we await trials comparing less conservative HbA1c treatment targets for older adults on patient-centered outcomes, the next best available study design is the prospective or retrospective cohort. Although cohort studies suffer from selective attrition and latent variable bias (unmeasured confounding), they may be useful in investigating potential linkages between intermediate outcomes often studied in randomized controlled trials (e.g. HbA1c control or albuminuria) and rate of downstream complications patients care about (e.g. death, end-stage renal disease). These links are generally assumed, but often not empirically supported.[60]

Finally, the current study suggests that most of the variation in the decision to intensify medication therapy is not related to patient factors, but idiosyncratic, unmeasured clinician decision-making heuristics. Primary care physician decision-making tools for older adults with multiple chronic conditions are needed[124] and are currently being developed.[125] The extent to which their use allows physicians to individualize care and reduce unnecessary treatment intensification remains to be seen, particularly in the face of "one-size-fits-all" performance markers.[126]

11 Paper 2. Choice of Second Line Antihyperglycemic Therapy for Older People with Type 2 Diabetes, Cognitive Impairment, and Cardiovascular Disease

Introduction

Almost ten years ago, three large trials found tight glycemic control increased the rate of serious iatrogenic hypoglycemic events among middle-aged people with type 2 diabetes and underlying cardiovascular risk factors.[32, 51, 52] Studies have since shown the risk of hypoglycemic events requiring hospitalization now exceeds the risk of acute hyperglycemic events of similar severity for adults over 60 years old,[5, 23] and the risk of serious hypoglycemic events increase with age, disease duration, cardiovascular disease, and sulfonylurea or insulin use.[127, 128] The American Diabetes Association (ADA) and the American Geriatrics Society (AGS) recommend less stringent glycated hemoglobin (HbA1c) targets for older adults with longstanding disease, physical or cognitive impairments, or multiple comorbidities or important complications that limit life expectancy.[7, 66]

Clinicians may also choose medications to reduce the risk of iatrogenic hypoglycemia. Metformin, a biguanide, is the widely accepted first-line treatment for hyperglycemia in type 2 diabetes, primarily because it does not cause weight gain, carries a low risk of hypoglycemia, and it is relatively inexpensive.[47, 91]

However, important to this study, combination therapies differ in their hypoglycemic risk profiles. Compared to other combination therapies, people taking Metformin in combination with either a second-generation sulfonylurea or long-acting insulin are at greater risk of hypoglycemic events. People taking Metformin and a sulfonylurea are almost 6 times more likely to have a mild to moderate hypoglycemic event than those taking Metformin and thiazolidinedione, pooled OR of 5.8 (95% CI 4.3 to 7.7).[47] People taking Metformin and a sulfonylurea were 33% more likely to have a hypoglycemic event compared to those taking Metformin and DPP-4.[92] People taking Metformin and a

sulfonylurea had 5 times as many hypoglycemic events as those taking Metformin and GLP-1 receptor agonists (5.32 versus .29 episodes per year).[93] Insulin has the highest rate of severe iatrogenic events of all therapies for type 2 diabetes.[33] Although sulfonylureas and insulins increase the risk of hypoglycemic events, they are the oldest and cheapest options (particularly sulfonylurea) for treating hyperglycemia. Table 2.1. compares combination therapies (adapted from ADA (2016) Approaches to Glycemic Management).[33]

The objective of this research is to determine how patient characteristics associated with an increased risk of iatrogenic hypoglycemia, age/disease duration, cognitive impairment, and cardiovascular disease, affect a primary care clinician's choice of second-line medication. We designed a vignette study in which we systematically varied these patient factors at two policy-relevant HbA1c levels: 7.5% and 8.5%.

Methods

This study used factorial survey methodology to analyze clinician decision making. The aim of vignettes is to make explicit or standardize the information respondents use to come to a decision. Survey respondents were presented a systematically constructed scenario, or vignette, and asked to rate the vignette on a pre-specified dimension. In this case, respondents were asked to choose one of six, second-line combination therapies for the treatment of hyperglycemia in response to poor glycemic control after six months of first-line, Metformin therapy.

Vignette Design

Patient hemoglobin level, age/disease duration, presence of cognitive impairment, and history of coronary artery disease with a previous coronary artery bypass graft (CABG) were randomly varied in the vignettes. Each patient factor had two levels (Table 2.2), yielding 16 possible vignette combinations. Patient gender, comorbid hypertension, body mass index, adequate glomerular filtration rate, mild neuropathic symptoms, lack of depression history, and medication affordability were held constant across vignettes. Five surnames that are common to both African Americans and Caucasians were used in an effort not to cue race or ethnicity. Each respondent viewed four, randomly selected

vignettes. A sample vignette and the response set are provided as Figure 2.1. A priori, we expected clinicians would choose second-line therapies with lower hypoglycemic risks and few side-effects (DPP-4 or GLP-1) for the 80-year-old with long-standing disease, coronary artery disease and cognitive impairment. Thiazolidinedione may increase the risk of congestive heart failure.[47] We expected clinicians would avoid this medication, particularly for patients with coronary artery disease.

Measures

Five choices of second-line combination therapies were provided to respondents:

1. **Metformin** (Glucophage) + **Sulfonylurea** (Glipizide, Glyburide, Amaryl)
2. **Metformin** (Glucophage) + **Thiazolidinedione** (Pioglitazone, Actos)
3. **Metformin** (Glucophage) + **DPP-4 Inhibitor** (Januvia, Onglyza)
4. **Metformin** (Glucophage) + **GLP-1 Receptor Agonist** (Exentide, Liraglutide)
5. **Metformin** (Glucophage) + **Long-Acting Insulin** (Lantus, Glargine, Detemir, Levemir)

Sodium glucose cotransporter (SGLT) 2 inhibitors were not in widespread use at the time this survey was developed and piloted, and, therefore were not part of the choice set.

In addition to the patient characteristics that were systematically varied in the vignettes, a few clinician characteristics were also collected, including: year respondent finished professional education, average length of a routine visit (minutes), and percent of practice that is Medicare (<25%, 25-75%, >75%). We expected clinicians who were educated more recently or whose practice was predominately Medicare patients to be more familiar with tailored recommendations for older adults and, therefore, less likely to choose medications for older, more complex patients that increase the risk of severe iatrogenic hypoglycemia (insulin and sulfonylureas) We also investigated the effects of clinician type (family medicine physicians, internal medicine physicians and nurse practitioners) and routine visit length on second-line medication choice.

Data & Sample

Data was collected between August and December, 2015. The 366 respondents included attendees of a state-level professional association meeting (n=20), members of AHRQ's practice-based research networks (n=83), and primary care physicians and nurse

practitioners emailed using state licensure lists for Minnesota and Florida (n=261). To be eligible, physicians and nurse practitioners had to be actively practicing primary care medicine at least 75% of the time. While geriatricians and specialists offer important perspectives on medication management for diabetics, this study focused on generalists and excluded specialists. Respondents attending a state professional association meeting completed the vignette survey in-person. Respondents from the practice-based research networks and those directly contacted were invited to participate by an email and completed the survey online. All responses were collected anonymously using Qualtrics software.

Analyses

The effect of vignette characteristics on medication choice was considered bivariately and using multivariate regression. Clinician variables were included in the regression models. The regression model chosen for this analysis was multinomial probit. Multinomial probit regression is a good choice for this analysis because it allows for modeling a categorical outcome (medications) while accounting for the panel nature of the data (clinicians viewing more than one vignette). The limitation of this model is that it assumes the independence of irrelevant alternatives (IIA). This means, if you remove one drug choice from the set, the remaining alternatives are equally likely to be chosen. In Appendix 2.A., we run an alternative model (mixlogit) which allows for each clinician to have a unique choice set through random coefficients. This model yields similar results to the chosen model. Finally, we collapsed the second-line medication choices into medications with greater risk of iatrogenic hypoglycemia (sulfonylureas and insulin) and those with less risk of iatrogenic hypoglycemia (TZD, GLP, DPP-4). For this, secondary analysis, we used a mixed effects probit model. Vignette and clinician characteristics were entered into the model as fixed effects, with a random intercept for each physician. This model allowed us to consider the intraclass correlation, or the strength of idiosyncratic clinician effects (e.g. chose the same drug for all four vignettes viewed). All analyses were conducted using Stata v.14.

Results

366 clinicians from 36 states participated, with the majority of respondents practicing in Minnesota (35% of sample) or Florida (26% of sample). 366 respondents responded to four vignettes and were included in the initial analytic sample. 30 surveys (8% of respondents) were excluded because their self-reported specialty was: "other" or not provided (n=11), geriatric or palliative care (n=9), endocrinology or nephrology (n=10). While geriatricians and specialists offer important perspectives on medication management for diabetics, this study focused on generalists who provide most of the diabetes care for older adults in this country.[129, 130] Respondent characteristics for the 108 family medicine physicians, 73 internal medicine physicians, and 155 nurse practitioners who completed the survey are provided in Table 2.3.

Each clinician viewed four vignettes, yielding 1,344 observations. An additional second-line medication was added for 953 of the 1,344 (71% of the time). Factors affecting treatment intensification have been previously reported. (Paper 1) The most popular second-line treatments were DPP4s (35%) and second-generation sulfonylureas (34%), followed by long-acting insulin (13%), GLPs (10%) and TZDs (7%). Table 2.4 shows bivariate comparison of second-line mediation choice by vignette factors. HbA1c and cognitive impairment appeared to affect medication choice. Hypothetical patients with higher HbA1c levels were more likely to receive insulin; hypothetical patients with cognitive impairment were less likely to receive long-acting insulin. Age and cardiovascular complications were not significantly related to medication choice in the bivariate analysis.

Results from the multinomial probit were similar to the bivariate analysis (Table 2.5). Having a HbA1 level of 8.5% compared to 7.5% increased the probability of choosing insulin by 6 percentage points (95% CI:1-12) and decreased the probability of choosing DPP4 by 7 percentage points (95% CI:1-14). Being 80 with long disease duration compared to 65 with shorter disease duration increased the probability of choosing DPP4 by 9 percentage points (95% CI:2-15). Having cardiovascular disease with a previous coronary artery bypass graft compared to no history of cardiovascular complications had

no significant impact on second-line medication choice. The strongest patient effects were seen for cognitive impairment. Presence of cognitive impairment decreased the probability of choosing insulin or GLP (7 and 4 percentage points respectively), and increased the probability of choosing TZD or DPP4 (4 and 8 percentage points respectively).

Internal medicine clinicians were significantly more likely to choose sulfonylureas than nurse practitioners and family practice physicians. Clinicians finishing their professional education more recently were more likely to choose sulfonylureas and less likely to choose insulin and DPP4. No significant differences in second-line medication choice by length of routine visit or percent of practice that is Medicare were observed. Using a mixed effects probit regression, we re-estimated the model collapsing second-line antihyperglycemic medication choices into those that increased hypoglycemic risk (insulin or sulfonylureas) and those with less risk of iatrogenic hypoglycemic risk (GLP, DPP4 or TZD). A hypothetical 80-year-old woman with longstanding diabetes, cognitive impairment, and coronary artery disease requiring bypass was recommended second-line therapy with either a second-generation sulfonylurea or long-acting insulin 45% of the time (95% CI: 36-51%) at a HbA1c of 8.5%, and 36% of the time (95% CI:29-44%) at a HbA1c of 7.5%. A hypothetical 65-year-old woman with relatively short duration diabetes, no cognitive impairment, and no history of heart disease had their treatment intensified with a sulfonylurea or insulin 58% of the time (95% CI:51-64%) at a HbA1c of 8.5%, and 50% of the time (95% CI:42-57%) at a HbA1c of 7.5%. Choice of insulin or sulfonylurea was not statistically different between otherwise healthy and the most complex patients in this population (Figure 2.2).

Discussion

Respondents in this sample were more likely to choose DPP4, a newer drug with a lower reported risk of hypoglycemia, for older patients with longstanding diabetes and cognitive impairment. However, the probability of intensification with a sulfonylureas or insulin (agents known to increase the risk of iatrogenic hypoglycemia), for an 80-year with longstanding diabetes, cognitive impairment and a coronary artery disease requiring

CABG, was 36% at a HbA1c level of 7.5% and 44% at a HbA1c level of 8.5%. Further, the rates of intensification with one of these two medications known to increase the hypoglycemia is lower in the current study than has been previously observed. Feil et al. (2011) found providers in the VA system prescribed insulin for patients with diabetes and cognitive impairment at higher rates than for patients without cognitive impairment.[131] Thorpe (2015) found 75% of VA patients with tightly controlled hyperglycemia (<7%) were prescribed either a sulfonylurea or insulin and older patients with vascular disease were more likely to receive these drugs.[120]

There are likely a few reasons our findings differ from observational studies. First, the vignettes stated the patient could afford her medications. DPP-4 inhibitors are newer (entered the market in 2006) and expensive, more than $300 per month.[22] Cost of medications is a concern for Medicare recipients with multiple chronic conditions who reach the Part D donut hole.[132, 133] Even traditionally cheaper drugs, like insulin, have seen unprecedented price hikes for consumers in the past ten years (300% increase to consumers).[134] The affordability of medications cannot be assumed in practice, as in this study.

Another way in which this research differs from practice is the focus on intensification versus de-intensification. Some clinicians may treat aggressively with insulin, earlier in the disease course, in order to alter the course of disease progression by protecting the β-cell,[135-137] although this is controversial.[138] Other clinicians may treat insulin as a treatment of last resort, when glycemic control cannot be achieved with oral medications. In the current study, higher HbA1 (8.5% versus 7.5%) was independently associated with insulin use, and younger patients with shorter disease were more likely to have their treatment intensified with insulin. Whether as an aggressive early treatment or last resort, in practice many 80-year-olds with longstanding disease will be on insulin (unlike the current study in which the older patient with longstanding disease remained on first-line therapy). Focusing on de-intensification of insulin as a patient ages and accumulates more of the complications of the disease should be a focus of future research. We know

that de-intensification rates are low; deintensification occurs about a quarter of the time, even for those with very low HbA1c levels (<6.5%).[86]

The AGS publishes a list of potentially inappropriate medications to be avoided in the older adults population, called the Beers Criteria.[139] The current list recommends against the use of short-acting insulins and glyburide, due to the high hypoglycemic risk. This study is limited in considering safer alternatives within the sulfonylurea class, as we combined safer alternatives, short-acting sulfonylureas (glipizide, gliclazide),[140] and glyburide in the same response category. We also considered only long-acting insulin. We are, therefore, not able to distinguish between intensification with safer alternatives within the same class.

Combination therapy continues to grow in popularity,[141] largely through the introduction of "better," newer drugs and an emphasis on intermediate HbA1c control through performance metrics and existing guidelines.[33] First-line treatment, Metformin, continues to be the cheapest and safest option. Evidence suggests the first anti-glycemic medication gives you the most "bang for your buck" and secondary treatments, meant to achieve tighter control, may result in increased adverse events (including unplanned hospitalizations) and drug-drug interactions.[22, 84, 85] Choosing a second-line medication to reduce hypoglycemic risk is a secondary conversation to getting clinicians to accept higher HbA1c levels for more complex patients with limited life expectancy who face more harms and few benefits from aggressive care.

12 Paper 3. Clinicians' Beliefs about Adherence Do Not Affect their Decisions to Intensify Medication Therapy for Older Adults with Cognitive Impairment

Background

For otherwise healthy adults with diabetes, physicians prescribe medications to achieve near-normal glycemic control and slow the downstream micro- and macrovascular complications associated with prolonged hyperglycemia. However, for older adults with longstanding diabetes tight glycemic control can often come at the cost of increased risk of iatrogenic hypoglycemia.[6, 112] Among Medicare recipients, rates of hospitalization for low blood sugar, or hypoglycemia, now exceed the rates of hospitalization for high blood sugar, or hyperglycemia.[6] Hypoglycemic related hospital use is costly, and affects the quality of life for older adults with diabetes.[24, 142]

People with diabetes and impaired cognition are more likely to have a hypoglycemic event resulting in medical care than those without impaired cognition.[88, 118, 143] Cognitive impairment has been linked to poorer adherence among older adults.[144, 145] Poor adherence may be linked to hypoglycemic events if a person administers an incorrect or additional dose of an anti-hyperglycemic agent, particularly insulin.[24] For this reason, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have recommended a patient-centered approach to hyperglycemic management, including setting less stringent HbA1c targets for people with type 2 diabetes who have more difficulty adhering to their medication regimes or have difficulties with self-care.[146] However, recent evidence suggests that older patients with diabetes and cognitive impairment were more tightly controlled than patients without cognitive impairment.[118]

In order to improve clinician behavior, we need to understand how they are making decisions. Clinician adherence predictions become important because adherence information is not universally obtained during patient encounters. A study of audiotaped clinic visits found adherence was mentioned by either the physician or the patient for 62 percent of prescribed medications.[98] Forty percent of these adherence discussions were initiated by the patients and most of the physician initiated inquiries consisted of simply asking the patient whether she takes her medications.[98] For the almost 40 percent of prescribed medications for which no adherence discussion occurs, clinicians are either not incorporating adherence information into their clinical decision making, or clinicians are substituting their own beliefs or predictions about likely patient adherence for patient-reported adherence information. Unfortunately, physicians are not very good at predicting adherence. Doctors correctly predict nonadherence only 25-35 percent of the time.[147, 148] Translation of patient-centered guidelines to practice requires physicians to recognize patient factors associated with nonadherence, including cognitive impairment.

In this vignette study we consider whether or not a clinician's belief about a patient's ability to self-manage their medications affects their decision to intensify medication therapy for a patient with cognitive impairment (Figure 3.1). Based on existing guidelines, we would expect clinicians to be less likely to intensify medication therapy (by adding a second-line medication therapy) for a patient with cognitive impairment, in part because of poorer predicted adherence.

The aims of this factorial vignette study are threefold:

1. To determine the degree to which patient cognitive impairment affects clinicians' adherence predictions;
2. To determine the degree to which patient cognitive impairment affects clinicians' decisions to intensify therapy; and
3. To determine whether or not adherence predictions partially mediate the decision to intensify anti-hyperglycemic medication therapy for people with diabetes and cognitive impairment.

We are also able to consider differences in adherence predictions and treatment intensification by primary care clinician type and respondent familiarity with serving older, more complex patients.

Methods

This study used factorial survey methodology to analyze clinician decision making. The aim of vignettes is to make explicit or standardize the information respondents use to come to a decision. Survey respondents were presented a systematically constructed scenario, or vignette, and asked to rate the vignette on a pre-specified dimension. In this case, respondents were asked to predict likely patient adherence to their medication recommendations and to recommend a medication therapy.

Vignette Design

Patient hemoglobin level, age/disease duration, presence of cognitive impairment, and history of coronary artery disease with a previous coronary artery bypass graft (CABG) were randomly varied in the vignettes. Each patient factor had two levels (Table 3.1.), yielding 16 possible vignette combinations. Patient gender, comorbid hypertension, body mass index, adequate glomerular filtration rate, mild neuropathic symptoms, lack of depression history, and medication affordability were held constant across vignettes. Five surnames that are common to both African Americans and Caucasians were used in an effort not to cue race or ethnicity. Each respondent viewed four, randomly selected vignettes. A sample vignette and the response set are provided as Figure 3.2. A priori, we expected clinicians to believe patients with cognitive impairment are less likely to adhere to their medications and, therefore, clinicians will be less likely to add an additional medication for hypothetical patients with cognitive impairment.

Measures

In response to each vignette, clinicians were asked to predict the likelihood of the hypothetical patient adhering to her medication regimen (very unlikely to adhere, somewhat unlikely to adhere, somewhat likely to adhere, very likely to adhere). However, we found only X% of clinicians predicted a patient would be very unlikely to adhere. For this reason, we collapsed predicted adherence from four categories (very

unlikely, somewhat unlikely, somewhat likely, very likely) to two categories (unlikely, likely).

Clinicians were also asked if they would intensify treatment for the hypothetical patient. Treatment intensification was defined as adding any one of five classes of approved second-line medication therapies. For the purposes of this analysis, a dichotomous variable was created to indicate intensification of medication therapy. Any choice other than continuing Metformin monotherapy was categorized as treatment intensification.

In addition to the patient characteristics that were systematically varied in the vignettes, a few clinician characteristics were also collected, including: year respondent finished professional education, average length of a routine visit (minutes), and percent of practice that is Medicare (<25%, 25-75%, >75%). We expected clinicians who were educated more recently or whose practice was predominately Medicare patients to be more familiar with tailored recommendations for older adults and, therefore, more likely to think patients with cognitive impairment would have difficulty adhering to medications and would be less likely to intensify therapy for those patients. We also investigated the effect of clinician type (family medicine physicians, internal medicine physicians and nurse practitioners) and routine visit length on the decision to intensify medication therapy.

Data & Sample

Data were collected between August and December, 2015. The 366 respondents included attendees of a state-level professional association meeting (n=20), members of AHRQ's practice-based research networks (n=83), and primary care physicians and nurse practitioners emailed using state licensure lists for Minnesota and Florida (n=261). To be eligible, physicians and nurse practitioners had to be actively practicing primary care medicine at least 75% of the time. While geriatricians and specialists offer important perspectives on medication management for diabetics, this study focused on generalists and excluded specialists. Respondents attending a state professional association meeting completed the vignette survey in-person. Respondents from the practice-based research

networks and those directly contacted were invited to participate by an email and completed the survey online. All responses were collected anonymously using Qualtrics software.

Analyses

We used mixed effects probit regression to consider the following partial mediation steps established by Baron and Kenny (1986)[149, 150]:

1. Cognitive impairment (X) must be significantly associated with treatment intensification (Y)
2. Cognitive impairment (X) must be significantly associated with predicted adherence (M)
3. Predicted adherence (M) must be significantly related to treatment intensification (Y) when both cognitive impairment and adherence are predictors of treatment intensification

If all three conditions are met, we used the difference of the effect of X on Y in the presence and absence of the mediator, or the indirect effect (c-c' or ab in Figure 6.), divided by the standard error of the difference, using a normal distribution to determine the statistical significance of the mediation effect. [149, 151] The significance will be formally tested using mediation will be formally tested using Sobel-Goodman test. For the mixed effects models, vignette and clinician characteristics were entered into the model as fixed effects, with a random intercept for each physician. This model allows us to consider the intra-class correlation, or the strength of idiosyncratic clinician effects (e.g. chose somewhat adherent for all vignettes). All analyses were conducted using Stata v.14.

Results

108 family medicine physicians, 73 internal medicine physicians, and 155 nurse practitioners from 36 states participated, with the majority of respondents practicing in Minnesota (35% of sample) or Florida (26% of sample). Each of the 366 respondents responded to four vignettes and were included in the initial analytic sample. 30 surveys (8% of respondents) were excluded because their self-reported specialty was: "other" or

not provided (n=11), geriatric or palliative care (n=9), endocrinology or nephrology (n=10). Respondent characteristics for the 108 family medicine physicians, 73 internal medicine physicians, and 155 nurse practitioners who completed the survey are provided in Table 3.2.

Respondents completed their professional education (medical school for physicians) between 1955 and 2015 (mean 1996). Internal medicine physicians had more years on average since finishing medical school (mean=1986). Nurse practitioners had fewer years since completion of their professional education (mean=2008). The length of a routine visit among responding clinicians varied from 5 to 90 minutes, with an average visit of 23 minutes in length. Average length of a routine visit was similar across clinician types. Respondents were also asked to estimate the percentage of their practice that is Medicare patients. 28% of sample, reported less than 25% percent of their practice was Medicare patients; 20% reported greater than 75% of their practice is Medicare; and 52% had between 25% and 75% of their practice consisting of Medicare patients. Nurse practitioners were the most likely to report having over 75% of their patient population enrolled in Medicare, followed by internal medicine physicians, and family medicine physicians.

Predicted Adherence

We first considered the effects of the patient characteristics varied in the vignettes on clinician predicted adherence (Table 3.3). Age, presence of coronary artery disease (CAD) with previous CABG, and HbA1c were not significantly associated with clinician adherence predictions. Cognitive Impairment (CI) was the only vignette variable significantly associated with clinician adherence predictions. Three percent of hypothetical patient vignettes without cognitive impairment were predicted to be unlikely to adhere by clinician respondents, compared to 21% of hypothetical patient vignettes with cognitive impairment. However, clinicians predicted 79% of patient vignettes with cognitive impairment would be likely or very likely to adhere.

Treatment Intensification

Next, we considered the effect of the same patient characteristics on a clinician's decision to add an additional medication, or intensify medication therapy. These results have been reported elsewhere (Paper 1). Briefly, clinicians were less likely to intensify treatment for hypothetical patients who were 80 years-old (versus 65), had cognitive impairment (compared to patients without cognitive impairment), or had a lower HbA1c (7.5% versus 8.5%). However, having coronary artery disease with previous CABG slightly increased the likelihood of treatment intensification, compared to hypothetical patients with no history of heart disease (Table 3.4).

Mediation

Our bivariate results indicated that patient cognitive impairment is negatively associated with clinician predicted adherence and a clinician's decision to intensify medication therapy. However, for predicted adherence to partially mediate the relationship between patient cognitive impairment and clinician decision to intensify medication therapy, the following criteria must be met:

1. Cognitive impairment (X) must be significantly associated with treatment intensification (Y)
2. Cognitive impairment (X) must be significantly associated with predicted adherence (M)
3. Predicted adherence (M) must be significantly related to treatment intensification (Y) when both cognitive impairment and adherence are predictors of treatment intensification

Table 3.5. shows the mixed effects probit regression results corresponding to each of these criteria.

Criteria 1. After controlling for other patient and provider characteristics, cognitive impairment was associated with an 11% (95% CI: 7%-14%) decrease in the likelihood of treatment intensification (Table 3.5, Model 1).

Criteria 2. After controlling for other patient and provider characteristics, cognitive impairment was also associated with an 18% (95% CI: 15%-22%) decrease in clinician predicted good adherence (Table 3.5, Model 2).

Criteria 3. Clinician predicted good adherence is associated with a 3% (95% CI: -3%-9%) nonsignificant increase in the probability of treatment intensification (Table 3.5, Model 3).

The direct effect of cognitive impairment on treatment intensification was a 11% decrease in treatment intensification (Pathway c in Figure 3.1. A.). When predicted adherence was added the model, the effect of cognitive impairment on treatment intensification was a 10% decrease in treatment intensification (Pathway c' in Figure 3.1.C.). Therefore, the indirect or partially mediated effect of cognitive impairment on treatment intensification through the pathway of predicted adherence was 1% (c-c'). Using the Sobel test for mediation,[152] we find that although adherence predictions explain about 10% of the total effect of cognitive impairment on the decision to intensify therapy, this partial mediation effect was not statistically significant (p= .10).

Discussion

Clinicians believed people with diabetes and cognitive impairment were less likely to adhere to their medication recommendations than people without cognitive impairment, and they were also less likely to intensify treatment for patients with cognitive impairment. However, predicted adherence did not explain clinicians' decisions not to intensify medication therapy for patients with cognitive impairment.

First, we acknowledge that adherence is a complex topic and we have a crude instrument. This paper focuses on only one potential barrier to adherence: memory-related adherence problems. People who have cognitive impairment may forget to take their medication,[153] or may take more medication than recommended.[96] There are multiple other reasons people may not take their medications as prescribed, including education or healthy literacy,[154, 155]cost-related barriers,[156] reluctance to change behaviors,[157] depression,[158-162] history of iatrogenic hypoglycemia,[163] and vision problems related to reading prescription labels.[164] None of these other types of

nonadherence are considered in this paper. Further, clinicians can improve adherence by providing patient education and changing the way medications are administered or dosed.[164-168] This study is limited in that we are not able to consider education, dosing or administration. It is possible that clinicians were less likely to incorporate their adherence predictions into their decision to intensify therapy because they believed they could address their adherence concerns by modifying dose or providing patient education. We also recognize the discussion to this point over-simplifies the relationship between hyperglycemia and cognitive impairment. The decision to intensify anti-glycemic medication therapy for a person with cognitive impairment is complicated by multi-directionality in the blood glucose-cognition relationship. People with type 2 diabetes and cognitive impairment are more likely to have severe hypoglycemic events (potentially through the impaired self-management pathway explored in this study). However, people with diabetes and a history of prior hypoglycemic events are also at greater risk for cognitive decline and dementia than those without a history of hypoglycemic events.[87, 88] Further, chronic high blood glucose, or hyperglycemia, also causes problems with cognition.[89]

We expected for younger patients with short disease duration, few micro- and macrovascular complications or comorbid conditions, and evidence of cognitive impairment, clinicians may more aggressively treat hyperglycemia (even with the risk of nonadherence). Being more aggressive earlier in the disease may reverse some of the cognition problems associated with hyperglycemia and slow insulin resistance. However, for older patients with long-standing disease who have accumulated more macrovascular disease and complications, as well as cognitive impairment, we expect providers' beliefs about adherence to have a greater effect on glycemic targets. (Figure 3.3). For this reason, we conducted a post-hoc analysis to determine whether adherence predictions had a stronger partial mediating effect on the decision to intensify medication therapy for older patients with longstanding disease. The indirect effect of predicted adherence on the decision to intensify therapy was the same as in the full sample (about 10% of total effect

of cognitive impairment on intensification), and the Sobel test for mediation was not significant (p =.24)

We are left to speculate as to why clinicians did not incorporate their adherence predictions into their treatment intensification decisions. It could be that clinicians had other, more dominant reasons for not intensifying treatment for a patient with cognitive impairment that were not adherence-related. The presence of cognitive impairment may be a strong signal of frailty.[169] Clinician beliefs about the futility of further treatment or fears about potential harms associated with aggressive care may provide more direct pathways between cognitive impairment and treatment intensification than through predicted adherence. Beliefs about treatment risks or treatment futility were not measured in the current study and warrant further study.

Clinicians may also be uncomfortable incorporating their beliefs or predictions into clinical decision-making. Clinicians are trained to believe that they act "objectively," without incorporating their beliefs or stereotypes into clinical decision-making.[170]

However, given half of what we do in medicine is based on inadequate evidence,[171] we should not be surprised that 35% of end-of-life spending and 12% of total US healthcare spending is associated with physician beliefs about doing less or more and not based on evidence of clinical benefit.[172] Further, adherence beliefs have been shown to enter into clinician decision-making in the case of pay-for-performance initiatives in which clinicians excluded patients who were unlikely to adhere to their medication regimens, in order to protect their financial incentives.[173] [174] If clinicians are not comfortable explicitly incorporating their adherence beliefs into their treatment decisions, patient-centered guidelines that ask clinicians to incorporate a patient's social support and ability to manage medications into treatment targets may be difficult for clinicians to implement.[146] Guidelines that provide recommendations based on clinical diagnosis alone may be more readily implemented than those that ask clinicians to consider the context in which that condition affects outcomes.

13 Summary of Findings

While we found some sensitivity to the patient factors mentioned in the existing guidelines, we also found evidence of overtreatment of the most complex hypothetical patients. For example, an 80-year-old with long standing diabetes, cognitive impairment, and coronary artery disease requiring bypass had a second-line treatment added 35% of the time at HbA1c of 7.5%, and 75% of the time at HbA1c of 8.5%. The same patient was recommended a sulfonylureas or insulin (agents known to increase the risk of iatrogenic hypoglycemia) 36% of the time at a HbA1c level of 7.5% and 44% at the time at a HbA1c level of 8.5%. Clinicians did not incorporate their adherence predictions into their decisions to intensify medication therapy. We found a few differences in practice patterns by clinician characteristics. Family practice physicians were less likely to intensify treatment than internal medicine physicians or nurse practitioners. This is likely to benefit the most complex patients who were the focus of this study. However, patients with shorter disease duration may be disadvantaged by the wait and see approach. Some variation in medication choice by clinician type was also observed.

Paper 1.

In paper 1 we considered the effects of vignette and clinician outcomes on the decision to intensify first-line Metformin therapy by adding an additional medication. HbA1c level, age / disease duration, and cognitive impairment significantly affected a clinicians' decision to intensify medication therapy. Having a higher HbA1c increased the probability of treatment intensification by 32 percent; being older with long-standing disease decreased the probability of treatment intensification by 21 percent; and having cognitive impairment decreased the probability of treatment intensification by 11 percentage points. Coronary artery disease with previous CABG was not significantly associated with the probability of intensification. The following two-way interactions were considered: HbA1c*age/disease duration, HbA1c*cognitive impairment, HbA1c*heart disease. Only the interaction between HbA1c and cognitive impairment

was significant; clinicians were more likely to accept a higher HbA1c for patients with cognitive impairment. Family medicine physicians were less likely to intensify therapy than nurse practitioners or internal medicine physicians. The most complex hypothetical patient, (an 80-year old with long diabetes duration, cognitive impairment and coronary artery disease), had a predicted probability of treatment intensification of 35% at HbA1c of 7.5% and 75% at HbA1c of 8.5%. Family medicine physicians were less likely than nurse practitioners or internal medicine physicians to intensify medication therapy for all patients. 60 percent of the variation in the decision to intensify medication therapy was due to individual physician behavior, not the patient factors varied in this study.

Paper 2.

In paper 2 we considered the effects of vignette and clinician outcomes on the choice of second-line medication therapy, if a clinician chose to intensify in paper 1. Clinicians intensified 71 % of the time (953 out of 1,344). The most popular second-line treatments were DPP4s (35%) and second-generation sulfonylureas (34%), followed by long-acting insulin (13%), GLPs (10%) and TZDs (7%). HbA1c level, age / disease duration, and cognitive impairment significantly affected a clinician's choice of second-line medication. Coronary artery disease with previous CABG was not significantly associated with the choice of medication. In general, having a higher HbA1c increased the probability of choosing insulin; being older with longer disease duration increased the probability of choosing DPP4; presence of cognitive impairment increased the probability of choosing TZD or DPP4 over insulin. Using an outcome of choosing a second-generation sulfonylurea or long-acting insulin, medications known to increase the risk of iatrogenic hypoglycemia, we found clinicians were 10 percentage points less likely to choose these medications for hypothetical patients with cognitive impairment and 6 percentage points less likely to choose these medications for older patients with longer disease duration. Higher HbA1c increased the likelihood of choosing insulin. The most complex hypothetical patient, (an 80-year old with long diabetes duration, cognitive impairment and coronary artery disease), had a predicted probability of having her treatment intensified with either a sulfonylurea or insulin of 36% at HbA1c of 7.5% and

50% at HbA1c of 8.5%. 80% of the variation in second-line medication choice was due to individual clinician behavior, not the patient factors varied in this study. Table 5 summarizes the findings from the first two papers.

Paper 3.

In paper 3 we asked whether clinician predicted adherence partially mediated the relationship between cognitive impairment and treatment intensification. For mediation to occur: 1. Cognitive impairment (X) must be significantly related to treatment intensification (Y); 2. Cognitive impairment (X) must be significantly associated with predicted adherence (mediator); and 3. Predicted adherence (M) must be significantly associated with treatment intensification. Conditions 1.and 2. were met, but condition 3. was not met. Clinicians believe patients with cognitive impairment are less likely than patients without cognitive impairment to adhere to their medications and clinicians are less likely to intensify medication therapy for hypothetical patients with cognitive impairment. However, clinicians' beliefs about likely patient adherence do not formally mediate their decisions to intensify medication therapy. Further, clinicians predicted patients with cognitive impairment were likely to adhere over 75% of the time. Clinicians may not be comfortable or accustomed to incorporating adherence predications into treatment decisions, or cognitive impairment may affect clinicians' decisions to intensify treatment through other pathways including perceived frailty. As primary care clinicians do not routinely discuss adherence with patients, guidelines that recommend clinicians consider a patient's ability to self-manage may be under-implemented.

14 Discussion and Implications

This work is part of a larger discussion around balancing the risks and benefits of aggressively treating hyperglycemia in older adults with type 2 diabetes for whom tight glycemic control produces few benefits and significantly increases risk for severe iatrogenic hypoglycemia. Clinicians have long known that hypoglycemia was a potentially severe side effect of antidiabetic treatment. However, the magnitude of this harm, particularly for older adults, has gained attention in the professional press[5, 22-25] and

coincides with a growing societal discussion about how we can live meaningful, less over-medicated older lives.[26, 27]

The magnitude of the potential overtreatment of hyperglycemia in this population is just beginning to be quantified, but likely exceeds 50% for older adults with multiple comorbid conditions (overtreatment variedly defined as actively controlled to HbA1c levels <7% or 7.5%).[86, 113, 119-121] We estimate overtreatment, defined as treatment intensification for the most complex hypothetical patents with HbA1c levels of 7.5%, to be around 35%. Our findings are directly aligned with a recent survey that found a third of primary care clinicians thought it would be difficult to follow the Choosing Wisely HbA1c recommendation for older adults, which states "Avoid using medications other than metformin to achieve hemoglobin A1c<7.5% in most older adults; moderate control is generally better."[113]

There are several reasons why clinicians may be over-treating this population and/or report having difficulty complying with existing guidelines. One barrier often described by physicians is the need to comply with existing performance metrics or pay-for-performance initiatives.[113] Pay for performance incentives, rewarding intermediate outcomes (HbA1c levels) below a certain threshold (e.g. <8%), are in wide-spread use.[175] There is some evidence that such incentives lead to over-testing or overtreatment,[176] which may be particularly harmful to older adults with multiple comorbid conditions. Another barrier to clinicians complying with existing guidelines is the fear of potential litigation in response to appropriate deintensification, or reducing medication burden as a person develops additional comorbid complications that limit life expectancy.[113] Education may be another barrier to appropriate treatment. There is a genuine lack of knowledge around the harms of overtreatment; 45% of primary care clinicians said they would not worry about potential harms from tight control (HbA1c of 6.5%) for a 77-year-old with longstanding type 2 diabetes with severe kidney disease taking glipizide (sulfonylurea).[113] Finally, the influence of the pharmaceutical market in overtreatment of hyperglycemia cannot be ignored. Profits from diabetes drugs grow by double digits every year based, in part, on the introduction of newer, "better" drugs and the more

aggressive treatment of hyperglycemia with two-drug combinations.[190] The associations setting guidelines are not independent from the pharmaceutical companies. Pharmaceutical companies are the largest corporate contributors to the ADA.[191]

Several policy options / approaches to reducing overtreatment have been proposed. Researchers from the University of Michigan, led by Jeremy Sussman, have focused on opportunities around de-intensification.[86] Intensive treatment is more appropriate early in the disease. As people age and accumulate more diabetes and other complications, it is likely that de-intensification should become a focus of diabetic care. However, currently, de-intensification occurs about a quarter of the time, even for those with very low HbA1c levels (<6.5%).[86] A policy option may be to provide incentives for appropriate de-intensification.[86] Incentives may also be provided for lower rates of iatrogenic hypoglycemia.[122] However, just as the current performance metrics have unintended consequences (potentially increased hypoglycemia in older, more complex patients), creating new metrics to reduce this harm may also have unintended consequences, including promoting the use of newer, more expensive drugs and devices.[122] Further, quality metrics targeting a reduction in iatrogenic hypoglycemia should not replace the need for quality metrics targeting hyperglycemia, as that could potentially result in an increase in under-treatment.

Another, not mutually exclusive, policy approach is to create guidelines that better address comorbidity. For older adults, one problem with tying pay-for-performance incentives to intermediate outcome measures for each chronic disease is older adults have multiple chronic diseases. 45% of men over the age of 65 have 2 or 3 chronic diseases; 17% have 4 or more chronic diseases.[55] 47% of women over the age of 65 have 2 or 3 chronic diseases; 16% have 4 or more chronic diseases.[55] For older adults with multiple comorbid conditions, these "one-size-fits-all" performance measures can result in polypharmacy and overtreatment.[177-181] The AGS and others have supported efforts to create recommendations to address multiple comorbid conditions,[125, 182-188] although there is little evidence on which to base these recommendations.[189] Medicare policy has the greatest ability to affect change in how multiple, disease-specific guidelines are applied

to complex populations. It remains to be seen whether the newest changes to Medicare reimbursement through the Medicare Access and CHIP Reauthorization Act (MACRA) will reinforce existing disease-specific metrics or begin to move us toward a more holistic, multi-morbidity framework.

15 Future Research

Although we are accumulating evidence of obvious overtreatment (near normal HbA1c targets for older adults with limited life expectancy), we do not know the effects of varying levels of intermediate control on longer-term outcomes in this more complex patient population. The ACCORD, ADVANCE, and VADT illuminated potential immediate or concurrent harms associated with attempting to achieve near-normal blood glucose control (HbA1c of <6.5%) in older patients with cardiac complications,[4, 52] but there are no randomized controlled trials exploring the long-term effects of managing more complex patients to the less stringent HbA1c targets mentioned in the existing guidelines (7.5%-9%).

While we await trials comparing HbA1c treatment targets between 7% and 8% to targets between 8% and 9% for older adults on patient-centered outcomes, the next best available study design is the prospective or retrospective cohort. Although cohort studies suffer from selective attrition and latent variable bias (unmeasured confounding), they can be particularly useful in investigating potential linkages between intermediate outcomes often studied in randomized controlled trials (e.g. HbA1c control or albuminuria) and rate of downstream complications patients care about (e.g. death, end-stage renal disease). These links are generally assumed, but not empirically supported.[60]

Future work, to be completed during the primary investigator's (EM's) post-doctoral appointment, will use medical claims data and electronic health record information to assign diabetic cases to one of three clinical complexity levels at baseline (based on the ADA/AGS guidelines): relatively heathy, complex/intermediate, and very complex/poor.[7] Then, we will consider the effects of varying levels of HbA1c control by complexity status at baseline on future, patient-centered outcomes including: hyper- and

hypoglycemic hospitalizations, cardiovascular events, and death (all-cause, cardiovascular, ESRD). This study will advance the literature by considering the effects of varying levels of glycemic control at varying levels of patient complexity over time. The results of this study will help us better define individualized care for patients who have already accumulated many of the microvascular and macrovascular complications of diabetes, for the purpose of maximizing their remaining quality of life.

Recent discussions of more aggressive blood pressure control, prompted by the Systolic Blood Pressure Intervention (SPRINT) Trial, may offer additional opportunities to analyze patient outcomes associated with various levels of control in complex, older adult populations.[192] Unlike the equivocal research surrounding glycemic control, treating hypertension and high cholesterol reduces the risk of macrovascular events (even in patients over 80 years old).[192, 193] A meta-analysis of 90,056 patients from 14 randomized controlled trials (RCTs) showed that diabetics 65 years and older (n=6446) treated with statin therapy to reduce high cholesterol had an 18% reduction in the risk of major cardiovascular events, similar to the 22% reduction in risk in younger populations. Statins are effective treatment independent of patient's age.[193] The Systolic Blood Pressure Intervention Trial (SPRINT) recently showed a reduction of fatal and nonfatal cardiovascular events with tight blood pressure control, even in those over 75 years of age, without a significant increase in harms.[192] Blood pressure and cholesterol control can also help slow the development of microvascular complications,[37, 42] but are not the focus of this particular study. Future work will consider the effects of varying levels of blood pressure and cholesterol control on downstream morbidity and mortality by patient age and clinical complexity.

16 References

1. Narayan KM, Boyle JP, Thompson TJ, et al. Lifetime risk for diabetes mellitus in the United States. JAMA. 2003 Oct 8;290(14):1884-90. PMID 14532317.

2. Control CfD, Prevention. National diabetes statistics report: estimates of diabetes and its burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services. 2014.

3. Vacante M, Malaguarnera M, Motta M. Revision of the ADA-classification of diabetes mellitus type 2 (DMT2): the importance of maturity onset diabetes (MOD), and senile diabetes (DS). Arch Gerontol Geriatr. 2011 Jul-Aug;53(1):113-9. PMID 20800300.

4. Punthakee Z, Miller ME, Launer LJ, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care. 2012 Apr;35(4):787-93. PMID 22374637.

5. Huang ES, Laiteerapong N, Liu JY, et al. Rates of Complications and Mortality in Older Diabetes Patients: The Diabetes and Aging Study. JAMA internal medicine. 2014;174(2):251-8. PMID PMC3950338.

6. Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. JAMA Intern Med. 2014 Jul;174(7):1116-24. PMID 24838229.

7. Association AD. 10. Older Adults. Diabetes Care. 2016 January 1, 2016;39(Supplement 1):S81-S5.

8. American Geriatrics Society Expert Panel on the Care of Older Adults with Diabetes M. Guidelines Abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 Update. Journal of the American Geriatrics Society. 2013;61(11):2020-6. PMID PMC4064258.

9. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in Older Adults. Diabetes Care. 2012 December 1, 2012;35(12):2650-64.

10. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 April 19, 2012.

11. Fried TR, Tinetti ME, Iannone L. Primary Care Clinicians' Experiences with Treatment Decision-Making for Older Persons with Multiple Conditions. Archives of internal medicine. 2011;171(1):75-80. PMID PMC3021478.

12. Schappert S, Rechtsteiner E. Ambulatory medical care utilization estimates for 2007. Vital and Health Statistics. Series 13, Data from the National Health Survey. 2011(169):1.

13. Chiang L. The geriatrics imperative: Meeting the need for physicians trained in geriatric medicine. JAMA. 1998;279(13):1036-7.

14. Boult C, Counsell SR, Leipzig RM, et al. The Urgency Of Preparing Primary Care Physicians To Care For Older People With Chronic Illnesses. Health Affairs. 2010 May 1, 2010;29(5):811-8.

15. Joyce GF, Carrera MP, Goldman DP, et al. Physician prescribing behavior and its impact on patient-level outcomes. Am J Manag Care. 2011 Dec;17(12):e462-71. PMID 22216870.

16. Gigerenzer G, Gaissmaier W. Heuristic Decision Making. Annual Review of Psychology. 2011;62(1):451-82. PMID 21126183.
17. Jasso G. Factorial Survey Methods for Studying Beliefs and Judgments. Sociological Methods & Research. 2006 February 1, 2006;34(3):334-423.
18. Feldman HA, McKinlay JB, Potter DA, et al. Nonmedical influences on medical decision making: an experimental technique using videotapes, factorial design, and survey sampling. Health Serv Res. 1997 Aug;32(3):343-66. PMID 9240285.
19. Hennessy M, MacQueen K, McKirnan DJ, et al. A factorial survey study to assess the acceptability of HIV vaccine trial designs. Controlled Clinical Trials. 1996;17(3):209-20.
20. Taylor BJ. Factorial Surveys: Using Vignettes to Study Professional Judgement. British Journal of Social Work. 2006 October 2006;36(7):1187-207.
21. Ludwick R, Zeller RA. The Factorial Survey: An Experimental Method to Replicate Real World Problems. Nursing Research. 2001;50(2):129-33.
22. Lipska KJ, Krumholz H, Soones T, et al. Polypharmacy in the Aging Patient: A Review of Glycemic Control in Older Adults With Type 2 Diabetes. JAMA. 2016;315(10):1034-45. PMID PMC4823136.
23. Lipska KJ, Ross JS, Wang Y, et al. NAtional trends in us hospital admissions for hyperglycemia and hypoglycemia among medicare beneficiaries, 1999 to 2011. JAMA internal medicine. 2014;174(7):1116-24.
24. Geller AI, Shehab N, Lovegrove MC, et al. NAtional estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. JAMA Internal Medicine. 2014;174(5):678-86.
25. Abdelhafiz AH, Rodríguez-Mañas L, Morley JE, et al. Hypoglycemia in Older People - A Less Well Recognized Risk Factor for Frailty. Aging and Disease. 2015;6(2):156-67. PMID PMC4365959.
26. Gawande A. Being mortal: Medicine and what matters in the end: Macmillan; 2014.
27. Sacks O. The joy of old age (no kidding). The New York Times. 2013:12.
28. Group NDD. Classification and Diagnosis of Diabetes Mellitus and Other Categories of Glucose Intolerance. Diabetes. 1979 December 1, 1979;28(12):1039-57.
29. Diabetes mellitus. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1985;727:1-113. PMID 3934850.
30. Association AD. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2012 January 1, 2012;35(Supplement 1):S64-S71.
31. Buse JB. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial: Design and Methods. American Journal of Cardiology.99(12):S21-S33.
32. Group TAC. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. New England Journal of Medicine. 2008;358(24):2560-72. PMID 18539916.
33. Association AD. 7. Approaches to Glycemic Treatment. Diabetes Care. 2016 January 1, 2016;39(Supplement 1):S52-S9.
34. Wray LA, Ofstedal MB, Langa KM, et al. The effect of diabetes on disability in middle-aged and older adults. J Gerontol A Biol Sci Med Sci. 2005 Sep;60(9):1206-11. PMID 16183964.
35. Spiers NA, Matthews RJ, Jagger C, et al. Diseases and impairments as risk factors for onset of disability in the older population in England and Wales: findings from the Medical Research Council Cognitive Function and Ageing Study. J Gerontol A Biol Sci Med Sci. 2005 Feb;60(2):248-54. PMID 15814870.

36. Wong E, Backholer K, Gearon E, et al. Diabetes and risk of physical disability in adults: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2013 Oct;1(2):106-14. PMID 24622316.
37. Boulton AJM, Malik RA, Arezzo JC, et al. Diabetic Somatic Neuropathies. Diabetes Care. 2004 June 1, 2004;27(6):1458-86.
38. Mayfield JA, Sugarman JR. The use of the Semmes-Weinstein monofilament and other threshold tests for preventing foot ulceration and amputation in persons with diabetes. J Fam Pract. 2000 Nov;49(11 Suppl):S17-29. PMID 11093555.
39. Ndip A, Lavery LA, LaFontaine J, et al. High Levels of Foot Ulceration and Amputation Risk in a Multiracial Cohort of Diabetic Patients on Dialysis Therapy. Diabetes Care. 2010 April 1, 2010;33(4):878-80.
40. McInnes A, Jeffcoate W, Vileikyte L, et al. Foot care education in patients with diabetes at low risk of complications: a consensus statement. Diabetic Medicine. 2011;28(2):162-7. PMID PMC3040291.
41. van Houtum WH. Barriers to the delivery of diabetic foot care. Lancet. 2005 Nov 12;366(9498):1678-9. PMID 16291048.
42. Massin P, Kaloustian E. The elderly diabetic's eyes. Diabetes Metab. 2007 Apr;33 Suppl 1:S4-9. PMID 17702094.
43. Saran R, Li Y, Robinson B, et al. US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2016 Mar;67(3 Suppl 1):A7-8. PMID 26925525.
44. Nephropathy in Diabetes. Diabetes Care. 2004 January 1, 2004;27(suppl 1):s79-s83.
45. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. Clinical Diabetes. 2008 April 1, 2008;26(2):77-82.
46. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA. 2002 May 15;287(19):2570-81. PMID 12020339.
47. Bennett WL, Wilson LM, Bolen S, et al. Oral diabetes medications for adults with type 2 diabetes: an update. 2011.
48. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care. 2009;32(1):187-92. PMID PMC2606812.
49. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011 2011-07-26 22:34:50;343.
50. Giorgino F, Leonardini A, Laviola L. Cardiovascular disease and glycemic control in type 2 diabetes: now that the dust is settling from large clinical trials. Annals of the New York Academy of Sciences. 2013;1281(1):36-50. PMID PMC3715107.
51. Group TAtCCRiDS. Effects of Intensive Glucose Lowering in Type 2 Diabetes. New England Journal of Medicine. 2008;358(24):2545-59. PMID 18539917.
52. Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. New England Journal of Medicine. 2009;360(2):129-39. PMID 19092145.

53. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). The Lancet.352(9131):837-53.
54. King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. British Journal of Clinical Pharmacology. 1999;48(5):643-8. PMID PMC2014359.
55. Ward BW, Schiller JS. Prevalence of Multiple Chronic Conditions Among US Adults: Estimates From the National Health Interview Survey, 2010. Preventing Chronic Disease. 2013;10:E65.
56. Gerstein HC, Riddle MC, Kendall DM, et al. Glycemia treatment strategies in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007 Jun 18;99(12A):34i-43i. PMID 17599423.
57. Boyko EJ. ACCORD Glycemia Results Continue to Puzzle. Diabetes Care. 2010 May 1, 2010;33(5):1149-50.
58. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010;340:b4909. PMID 20061358.
59. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. The Lancet.376(9739):419-30.
60. Yudkin JS, Lipska KJ, Montori VM. The idolatry of the surrogate. BMJ. 2011 2011-12-28 11:22:21;343.
61. Dhar GC. Intensive glycemic control: Implications of the ACCORD, ADVANCE, and VADT trials for family physicians. Canadian Family Physician. 2009;55(8):803-4. PMID PMC2726096.
62. Introduction. Diabetes Care. 2016 January 1, 2016;39(Supplement 1):S1-S2.
63. Association AD. 1. Strategies for Improving Care. Diabetes Care. 2016 January 1, 2016;39(Supplement 1):S6-S12.
64. Standards of Medical Care in Diabetes—2016: Summary of Revisions. Diabetes Care. 2016 January 1, 2016;39(Supplement 1):S4-S5.
65. Association AD. 5. Glycemic Targets. Diabetes Care. 2016 January 1, 2016;39(Supplement 1):S39-S46.
66. Huang ES, Davis AM. Glycemic Control in Older Adults With Diabetes Mellitus. JAMA. 2015;314(14):1509-10. PMID PMC4620041.
67. Usha Subramanian MD M, Neha Gavin MD M, Traylor A, et al. The association of patient age with cardiovascular disease risk factor treatment and control in diabetes. Journal of General Internal Medicine. 2009;24(9):1049-52.
68. Meneilly GS, Tessier D. Diabetes in elderly adults. J Gerontol A Biol Sci Med Sci. 2001 Jan;56(1):M5-13. PMID 11193234.
69. Thomson F, Masson E, Leeming J, et al. Lack of knowledge of symptoms of hypoglycaemia by elderly diabetic patients. Age and ageing. 1991;20(6):404-6.
70. Meneilly GS, Cheung E, Tuokko H. Altered responses to hypoglycemia of healthy elderly people. J Clin Endocrinol Metab. 1994 Jun;78(6):1341-8. PMID 8200936.
71. Chau D, Edelman SV. Clinical Management of Diabetes in the Elderly. Clinical diabetes. 2001 October 1, 2001;19(4):172-5.
72. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59. PMID 18539917.

73. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ. 2010;340:b5444. PMID 20061360.
74. Lipska KJ, Krumholz HM. Comparing diabetes medications: Where do we set the bar? JAMA Internal Medicine. 2014;174(3):317-8.
75. Schoenborn NL, Bowman TL, 2nd, Cayea D, et al. Primary Care Practitioners' Views on Incorporating Long-term Prognosis in the Care of Older Adults. JAMA Intern Med. 2016 Apr 11PMID 27064895.
76. Leal J, Gray AM, Clarke PM. Development of life-expectancy tables for people with type 2 diabetes. European Heart Journal. 2009;30(7):834-9. PMID PMC2663724.
77. Cho H, Klabunde CN, Yabroff KR, et al. Comorbidity-Adjusted Life Expectancy: A New Tool to Inform Recommendations for Optimal Screening Strategies. Annals of Internal Medicine. 2013;159(10):667-76.
78. McGuire LC, Ford ES, Ajani UA. The impact of cognitive functioning on mortality and the development of functional disability in older adults with diabetes: the second longitudinal study on aging. BMC Geriatrics. 2006;6(1):1-7.
79. Smith A, Schonberg M, Yourman L, et al. ePrognosis. 2011.
80. Christakis NA, Lamont EB. Extent and determinants of error in physicians' prognoses in terminally ill patients: prospective cohort study. Western Journal of Medicine. 2000;172(5):310-3. PMID PMC1070876.
81. Christakis NA, Lamont EB. Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study. BMJ. 2000 Feb 19;320(7233):469-72. PMID 10678857.
82. Boyd CM, Darer J, Boult C, et al. Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases. JAMA: The Journal of the American Medical Association. 2005 August 10, 2005;294(6):716-24.
83. Spinewine A, Schmader KE, Barber N, et al. Prescribing in elderly people 1—Appropriate prescribing in elderly people: how well can it be measured and optimised. Lancet. 2007;370(9582):173-84.
84. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. J Am Geriatr Soc. 2004 Aug;52(8):1349-54. PMID 15271125.
85. Marcum ZA, Amuan ME, Hanlon JT, et al. Prevalence of Unplanned Hospitalizations Caused by Adverse Drug Reactions Among Older Veterans. Journal of the American Geriatrics Society. 2012;60(1):34-41. PMID PMC3258324.
86. Sussman JB, Kerr EA, Saini SD, et al. RAtes of deintensification of blood pressure and glycemic medication treatment based on levels of control and life expectancy in older patients with diabetes mellitus. JAMA Internal Medicine. 2015;175(12):1942-9.
87. Feinkohl I, Aung PP, Keller M, et al. Severe Hypoglycemia and Cognitive Decline in Older People With Type 2 Diabetes: The Edinburgh Type 2 Diabetes Study. Diabetes Care. 2014 February 1, 2014;37(2):507-15.
88. Yaffe K, Falvey CM, Hamilton N, et al. ASsociation between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. JAMA Internal Medicine. 2013;173(14):1300-6.
89. Kodl CT, Seaquist ER. Cognitive Dysfunction and Diabetes Mellitus. Endocrine Reviews. 2008;29(4):494-511. PMID PMC2528851.

90. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and Cardiovascular Risks. Diabetes Care. 2011 May 1, 2011;34(Supplement 2):S132-S7.
91. Bodmer M, Meier C, Krähenbühl S, et al. Metformin, Sulfonylureas, or Other Antidiabetes Drugs and the Risk of Lactic Acidosis or Hypoglycemia: A nested case-control analysis. Diabetes Care. 2008 November 1, 2008;31(11):2086-91.
92. Raju A, Shetty S, Cai B, et al. Hypoglycemia Incidence Rates and Associated Health Care Costs in Patients with Type 2 Diabetes Mellitus Treated with Second-Line Linagliptin or Sulfonylurea After Metformin Monotherapy. J Manag Care Spec Pharm. 2016 May;22(5):483-92. PMID 27123911.
93. Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. Lancet. 2012 Jun 16;379(9833):2270-8. PMID 22683137.
94. Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. Diabetes Care. 2004;27(9):2149-53.
95. Insel K, Morrow D, Brewer B, et al. Executive Function, Working Memory, and Medication Adherence Among Older Adults. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 2006 March 1, 2006;61(2):P102-P7.
96. Winkler A, Teuscher AU, Mueller B, et al. Monitoring adherence to prescribed medication in type 2 diabetic patients treated with sulfonylureas. Swiss medical weekly. 2002;132(27-28):379-85.
97. Heisler M, Hogan MM, Hofer TP, et al. When More Is Not Better: Treatment Intensification Among Hypertensive Patients With Poor Medication Adherence. Circulation. 2008 June 3, 2008;117(22):2884-92.
98. Tarn DM, Mattimore TJ, Bell DS, et al. Provider Views About Responsibility for Medication Adherence and Content of Physician–Older Patient Discussions. Journal of the American Geriatrics Society. 2012;60(6):1019-26.
99. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. Archives of internal medicine. 2006;166(17):1836.
100. Jin J, Sklar GE, Min Sen Oh V, et al. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag. 2008 Feb;4(1):269-86. PMID 18728716.
101. Shari Bolen MD M, Abuid M, Marinopoulos SS, et al. Missed opportunities in diabetes management: a longitudinal assessment of factors associated with sub-optimal quality. Journal of General Internal Medicine. 2008;23(11):1770-7.
102. O'Connor PJ, Rush WA, Davidson G, et al. Variation in quality of diabetes care at the levels of patient, physician, and clinic. Prev Chronic Dis. 2008 Jan;5(1):A15. PMID 18082004.
103. Misbin RI. The Phantom of Lactic Acidosis due to Metformin in Patients With Diabetes. Diabetes Care. 2004 July 1, 2004;27(7):1791-3.
104. Ebell M. Link between metformin and lactic acidosis? Am Fam Physician. 2004 Dec 1;70(11):2109-10. PMID 15606058.
105. Cayley WE, Jr. Does metformin increase the risk of fatal or nonfatal lactic acidosis? Am Fam Physician. 2010 Nov 1;82(9):1068-70. PMID 21121550.

106. Snow J, Mann M. Qualtrics Survey Software. Handbook for Research Professionals. Obtenido de http://www. qualtrics. com; 2013.
107. Tilburt JC, Miller FG, Jenkins S, et al. Factors that influence practitioners' interpretations of evidence from alternative medicine trials: a factorial vignette experiment embedded in a national survey. Med Care. 2010 Apr;48(4):341-8. PMID 20355265.
108. Veloski J, Tai S, Evans AS, et al. Clinical Vignette-Based Surveys: A Tool for Assessing Physician Practice Variation. American Journal of Medical Quality. 2005 May/June 2005;20(3):151-7.
109. McEwen LN, Bilik D, Johnson SL, et al. Predictors and impact of intensification of antihyperglycemic therapy in type 2 diabetes: translating research into action for diabetes (TRIAD). Diabetes Care. 2009 Jun;32(6):971-6. PMID 19228862.
110. Subramanian U, Schmittdiel JA, Gavin N, et al. The Association of Patient Age with Cardiovascular Disease Risk Factor Treatment and Control in Diabetes. Journal of General Internal Medicine. 2009;24(9):1049-52. PMID PMC2726890.
111. Hicks R, Tingley D. Causal mediation analysis. Stata Journal. 2011;11(4):605.
112. Punthakee Z, Miller ME, Launer LJ, et al. Poor Cognitive Function and Risk of Severe Hypoglycemia in Type 2 Diabetes: Post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care. 2012;35(4):787-93. PMID PMC3308284.
113. Caverly TJ, Fagerlin A, Zikmund-Fisher B, et al. Appropriate prescribing for patients with diabetes at high risk for hypoglycemia: National survey of veterans affairs health care professionals. JAMA Internal Medicine. 2015;175(12):1994-6.
114. Lipska KJ, Krumholz H, Soones T, et al. Polypharmacy in the Aging Patient: A Review of Glycemic Control in Older Adults With Type 2 Diabetes. JAMA. 2016 Mar 8;315(10):1034-45. PMID 26954412.
115. Yau CK, Eng C, Cenzer IS, et al. Glycosylated hemoglobin and functional decline in community-dwelling nursing home-eligible elderly adults with diabetes mellitus. J Am Geriatr Soc. 2012 Jul;60(7):1215-21. PMID 22702660.
116. Peabody JW, Luck J, Glassman P, et al. Comparison of vignettes, standardized patients, and chart abstraction: a prospective validation study of 3 methods for measuring quality. JAMA. 2000 Apr 5;283(13):1715-22. PMID 10755498.
117. Lipska KJ, Ross JS, Miao Y, et al. POtential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Internal Medicine. 2015;175(3):356-62.
118. Feil DG, Rajan M, Soroka O, et al. Risk of Hypoglycemia in Older Veterans with Dementia and Cognitive Impairment: Implications for Practice and Policy. Journal of the American Geriatrics Society. 2011;59(12):2263-72.
119. Penfornis A, Fiquet B, Blicklé JF, et al. Potential glycemic overtreatment in patients ≥75 years with type 2 diabetes mellitus and renal disease: experience from the observational OREDIA study. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2015;8:303-13. PMID PMC4498726.
120. Thorpe CT, Gellad WF, Good CB, et al. Tight glycemic control and use of hypoglycemic medications in older veterans with type 2 diabetes and comorbid dementia. Diabetes Care. 2015 Apr;38(4):588-95. PMID 25592195.
121. Tseng CL, Soroka O, Maney M, et al. Assessing potential glycemic overtreatment in persons at hypoglycemic risk. JAMA Intern Med. 2014 Feb 1;174(2):259-68. PMID 24322626.
122. Rodriguez-Gutierrez R, Lipska KJ, McCoy RG, et al. Hypoglycemia as an indicator of good diabetes care. BMJ. 2016 2016-03-07 15:45:55;352.

123. Lipska KJ, Krumholz HM. Comparing diabetes medications: where do we set the bar? JAMA Intern Med. 2014 Mar;174(3):317-8. PMID 24366351.
124. Boyd CM, Darer J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA. 2005 Aug 10;294(6):716-24. PMID 16091574.
125. Fried TR, Niehoff K, Tjia J, et al. A Delphi process to address medication appropriateness for older persons with multiple chronic conditions. BMC Geriatr. 2016;16(1):67. PMID 26979576.
126. Hunt LM, Kreiner M, Brody H. The changing face of chronic illness management in primary care: a qualitative study of underlying influences and unintended outcomes. Ann Fam Med. 2012 Sep-Oct;10(5):452-60. PMID 22966109.
127. Pathak RD, Schroeder EB, Seaquist ER, et al. Severe Hypoglycemia Requiring Medical Intervention in a Large Cohort of Adults With Diabetes Receiving Care in U.S. Integrated Health Care Delivery Systems: 2005-2011. Diabetes Care. 2016 Mar;39(3):363-70. PMID 26681726.
128. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care. 2013 May 1, 2013;36(5):1384-95.
129. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. Vital Health Stat 13. 2011 Apr(169):1-38. PMID 21614897.
130. Chiang L. The geriatrics imperative: meeting the need for physicians trained in geriatric medicine. JAMA. 1998 Apr 1;279(13):1036-7. PMID 9533508.
131. Feil DG, Rajan M, Soroka O, et al. Risk of hypoglycemia in older veterans with dementia and cognitive impairment: implications for practice and policy. J Am Geriatr Soc. 2011 Dec;59(12):2263-72. PMID 22150156.
132. Lau DT, Briesacher BA, Touchette DR, et al. Medicare Part D and quality of prescription medication use in older adults. Drugs Aging. 2011 Oct 1;28(10):797-807. PMID 21970307.
133. Zhang Y, Baik SH, Lave JR. Effects of Medicare Part D coverage gap on medication adherence. Am J Manag Care. 2013 Jun;19(6):e214-24. PMID 23844750.
134. Naci H, Soumerai SB, Ross-Degnan D, et al. Medication Affordability Gains Following Medicare Part D Are Eroding Among Elderly With Multiple Chronic Conditions. Health Affairs. 2014 August 1, 2014;33(8):1435-43.
135. Niswender K. Early and Aggressive Initiation of Insulin Therapy for Type 2 Diabetes: What Is the Evidence? Clinical Diabetes. 2009 April 1, 2009;27(2):60-8.
136. Meneghini LF. Early Insulin Treatment in Type 2 Diabetes. What are the pros? 2009 2009-11-01 00:00:00;32(suppl 2):S266-S9.
137. Owens DR. Clinical evidence for the earlier initiation of insulin therapy in type 2 diabetes. Diabetes Technol Ther. 2013 Sep;15(9):776-85. PMID 23786228.
138. Chiasson J-L. Early Insulin Use in Type 2 Diabetes. What are the cons? 2009 2009-11-01 00:00:00;32(suppl 2):S270-S4.
139. By the American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society. 2015;63(11):2227-46.
140. Hanlon JT, Semla TP, Schmader KE. Alternative Medications for Medications in the Use of High-Risk Medications in the Elderly and Potentially Harmful Drug-Disease

Interactions in the Elderly Quality Measures. J Am Geriatr Soc. 2015 Dec;63(12):e8-e18. PMID 26447889.
141. Cohen FJ, Neslusan CA, Conklin JE, et al. Recent antihyperglycemic prescribing trends for US privately insured patients with type 2 diabetes. Diabetes Care. 2003 Jun;26(6):1847-51. PMID 12766121.
142. Lee SJ. So Much Insulin, So Much Hypoglycemia. JAMA Internal Medicine. 2014;174(5):686-8. PMID PMC4067162.
143. Zoungas S, Patel A, Chalmers J, et al. Severe Hypoglycemia and Risks of Vascular Events and Death. New England Journal of Medicine. 2010;363(15):1410-8. PMID 20925543.
144. Cooper C, Carpenter I, Katona C, et al. The AdHOC Study of older adults' adherence to medication in 11 countries. Am J Geriatr Psychiatry. 2005 Dec;13(12):1067-76. PMID 16319299.
145. Tomlin A, Sinclair A. The influence of cognition on self-management of type 2 diabetes in older people. Psychol Res Behav Manag. 2016;9:7-20. PMID 26855601.
146. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015 January 1, 2015;38(1):140-9.
147. Macintyre CR, Goebel K, Brown GV. Patient knows best: blinded assessment of nonadherence with antituberculous therapy by physicians, nurses, and patients compared with urine drug levels. Prev Med. 2005 Jan;40(1):41-5. PMID 15530579.
148. Mushlin AI, Appel FA. Diagnosing potential noncompliance: Physicians' ability in a behavioral dimension of medical care. Archives of Internal Medicine. 1977;137(3):318-21.
149. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation Analysis. Annual review of psychology. 2007;58:593. PMID PMC2819368.
150. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986 Dec;51(6):1173-82. PMID 3806354.
151. Mackinnon DP, Dwyer JH. Estimating Mediated Effects in Prevention Studies. Evaluation Review. 1993 April 1, 1993;17(2):144-58.
152. Sobel ME. Asymptotic Confidence Intervals for Indirect Effects in Structural Equation Models. Sociological Methodology. 1982;13:290-312.
153. Vedhara K, Wadsworth E, Norman P, et al. Habitual prospective memory in elderly patients with Type 2 diabetes: implications for medication adherence. Psychology, health & medicine. 2004;9(1):17-27.
154. Schillinger D, Piette J, Grumbach K, et al. Closing the loop: physician communication with diabetic patients who have low health literacy. Archives of internal medicine. 2003;163(1):83.
155. Lowry KP, Dudley TK, Oddone EZ, et al. Intentional and unintentional nonadherence to antihypertensive medication. The Annals of pharmacotherapy. 2005;39(7/8):1198-203.
156. Brown JB, Harris SB, Webster-Bogaert S, et al. The role of patient, physician and systemic factors in the management of type 2 diabetes mellitus. Fam Pract. 2002 Aug;19(4):344-9. PMID 12110552.

157. Huang ES, Gorawara-Bhat R, Chin MH. Self-Reported Goals of Older Patients with Type 2 Diabetes Mellitus. Journal of the American Geriatrics Society. 2005;53(2):306-11.
158. Katon WJ, Von Korff M, Lin EHB, et al. The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. Archives of General Psychiatry. 2004;61(10):1042.
159. Nau DP, Aikens JE, Pacholski AM. Effects of gender and depression on oral medication adherence in persons with type 2 diabetes mellitus. Gender medicine. 2007;4(3):205-13.
160. Kilbourne AM, Reynolds III CF, Good CB, et al. How does depression influence diabetes medication adherence in older patients? American Journal of Geriatric Psych. 2005;13(3):202.
161. Lin EHB, Katon W, Von Korff M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. Diabetes Care. 2004;27(9):2154-60.
162. Kalsekar ID, Madhavan SS, Amonkar MM, et al. Depression in patients with type 2 diabetes: impact on adherence to oral hypoglycemic agents. The Annals of pharmacotherapy. 2006;40(4):605-11.
163. Chao J, Nau DP, Aikens JE. Patient-reported perceptions of side effects of antihyperglycemic medication and adherence to medication regimens in persons with diabetes mellitus. Clinical Therapeutics. 2007;29(1):177-80.
164. Odegard PS, Gray SL. Barriers to medication adherence in poorly controlled diabetes mellitus. The Diabetes Educator. 2008;34(4):692-7.
165. Bangalore S, Kamalakkannan G, Parkar S, et al. Fixed-dose combinations improve medication compliance: a meta-analysis. The American journal of medicine. 2007;120(8):713-9.
166. Weymiller AJ, Montori VM, Jones LA, et al. Helping patients with type 2 diabetes mellitus make treatment decisions: statin choice randomized trial. Arch Intern Med. 2007 May 28;167(10):1076-82. PMID 17533211.
167. Hauber A, Mohamed A, Johnson F, et al. Treatment preferences and medication adherence of people with Type 2 diabetes using oral glucose-lowering agents. Diabetic Medicine. 2009;26(4):416-24.
168. Saini SD, Schoenfeld P, Kaulback K, et al. Effect of medication dosing frequency on adherence in chronic diseases. Methods. 2007.
169. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. The Lancet. 2013;381(9868):752-62.
170. Wilson HJ. The myth of objectivity: is medicine moving towards a social constructivist medical paradigm? Family Practice. 2000 April 1, 2000;17(2):203-9.
171. Garrow JS. How much of orthodox medicine is evidence based? BMJ. 2007 2007-11-08 23:00:54;335(7627):951-.
172. Cutler D, Skinner J, Stern AD, et al. Physician beliefs and patient preferences: a new look at regional variation in health care spending National Bureau of Economic Research. 2013.
173. McDonald R, Roland M. Pay for Performance in Primary Care in England and California: Comparison of Unintended Consequences. The Annals of Family Medicine. 2009 March 1, 2009;7(2):121-7.
174. Sigfrid L, Turner C, Crook D, et al. Using the UK primary care Quality and Outcomes Framework to audit health care equity: preliminary data on diabetes management. Journal of Public Health. 2006;28(3):221-5.

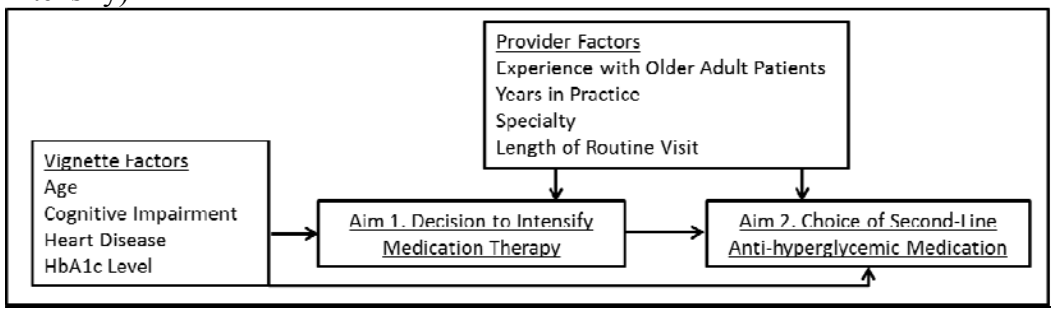
175. Epstein AM. Pay for Performance at the Tipping Point. New England Journal of Medicine. 2007;356(5):515-7. PMID 17259445.
176. McCoy RG, Van Houten HK, Ross JS, et al. HbA1c overtesting and overtreatment among US adults with controlled type 2 diabetes, 2001-13: observational population based study. BMJ. 2015;351:h6138. PMID 26646052.
177. Halanych JH, Safford MM, Keys WC, et al. Burden of Comorbid Medical Conditions and Quality of Diabetes Care. Diabetes Care. 2007 December 1, 2007;30(12):2999-3004.
178. Boyd CM, Darer J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: Implications for pay for performance. JAMA. 2005;294(6):716-24.
179. Roland M. Clinical practice guidelines for older patients with comorbid diseases. JAMA. 2006 Jan 4;295(1):33-4; author reply 4-5. PMID 16391208.
180. Tinetti ME, McAvay G, Trentalange M, et al. Association between guideline recommended drugs and death in older adults with multiple chronic conditions: population based cohort study. BMJ. 2015;351:h4984. PMID 26432468.
181. Goodman RA, Boyd C, Tinetti ME, et al. IOM and DHHS Meeting on Making Clinical Practice Guidelines Appropriate for Patients with Multiple Chronic Conditions. The Annals of Family Medicine. 2014 May 1, 2014;12(3):256-9.
182. Mutasingwa DR, Ge H, Upshur RE. How applicable are clinical practice guidelines to elderly patients with comorbidities? Can Fam Physician. 2011 Jul;57(7):e253-62. PMID 21753084.
183. Fabbri LM, Boyd C, Boschetto P, et al. How to integrate multiple comorbidities in guideline development: article 10 in Integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. Proc Am Thorac Soc. 2012 Dec;9(5):274-81. PMID 23256171.
184. Cox L, Kloseck M, Crilly R, et al. Underrepresentation of individuals 80 years of age and older in chronic disease clinical practice guidelines. Can Fam Physician. 2011 Jul;57(7):e263-9. PMID 21753085.
185. Hughes LD, McMurdo MET, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. Age and Ageing. 2013 January 1, 2013;42(1):62-9.
186. Tinetti ME, Esterson J, Ferris R, et al. Patient Priority–Directed Decision Making and Care for Older Adults with Multiple Chronic Conditions. Clinics in Geriatric Medicine.32(2):261-75.
187. Tinetti ME, Fried TR, Boyd CM. DEsigning health care for the most common chronic condition—multimorbidity. JAMA. 2012;307(23):2493-4.
188. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians: American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. J Am Geriatr Soc. 2012 Oct;60(10):E1-E25. PMID 22994865.
189. Fried TR, O'Leary J, Towle V, et al. The effects of comorbidity on the benefits and harms of treatment for chronic disease: a systematic review. PLoS One. 2014;9(11):e112593. PMID 25402463.
190. Hauber A, Gale EA. The market in diabetes. Diabetologia. 2006 Feb;49(2):247-52. PMID 16416145.
191. Santora M. In diabetes fight, raising cash and keeping trust. 2006.
192. Group TSR. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. New England Journal of Medicine. 2015;373(22):2103-16. PMID 26551272.

193. Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008 Jan 12;371(9607):117-25. PMID 18191683.

17 Figures & Tables

Figure 1. Conceptual Models

Model 1. Effect of Patient (Vignette) and Provider Factors on a Clinicians' Decision to Intensify Medication Therapy and Subsequent Choice of Second-Line Medication (if Intensify)



Model 2. Partially Mediating Effect of Clinician Predicted Adherence on the Decision to Intensify Medication Therapy

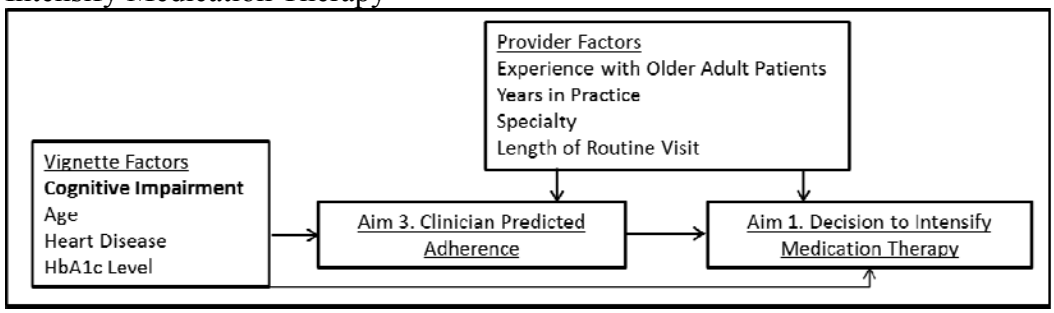


Figure 2. ADA 2016 General Recommendations for Glycemic Targets

- A reasonable A1C goal for many nonpregnant adults is 7% (53 mmol/mol).
- Providers might reasonably suggest more stringent A1C goals (such as 6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease.
- Less stringent A1C goals (such as 8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.

Adapted from ADA 2016 Recommendations, Chapter 5. Glycemic Targets, p. S41[65]

Figure 1.1. Sample Vignette

Mrs. Brown is **80 years old and has had type 2 diabetes for 15 years**. Three months ago, Mrs. Brown was prescribed Metformin 1000 mg (BID), an ACE inhibitor to control comorbid hypertension, and a low-dose aspirin. Mrs. Brown currently has a **HbA1c of 7.5%**, a BP of 140/80 mmHg, and a BMI of 29. Her basic metabolic profile is normal and GFR > 60. **Mrs. Brown has coronary artery disease, for which she underwent a coronary artery bypass graft five years ago**. Mrs. Brown reports an intermittent pain in her feet, but has difficulty localizing it. There is no history of depression. **Mrs. Brown has some recent memory loss on formal testing. She lives independently, but depends on her eldest daughter to keep her medical appointments and pay her bills. She stopped driving, in part because she occasionally got lost**. Mrs. Brown is able to afford her medications.

1. **Which anti-hyperglycemic treatment option are you most likely to recommend?** Mark only one.

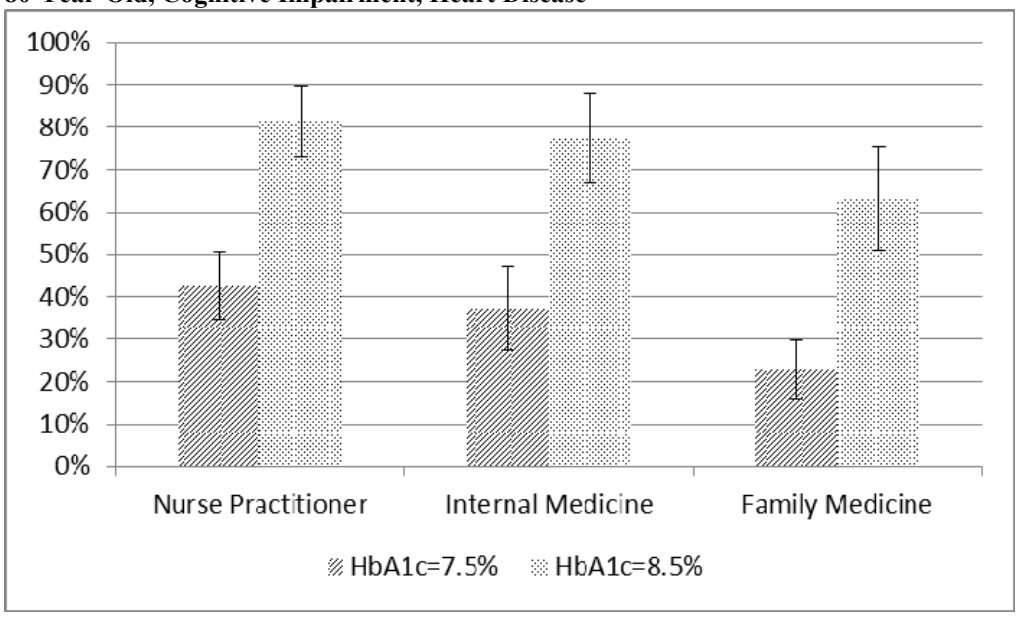
   - ☐ Continue **Metformin** (Glucophage) Monotherapy
   - ☐ **Metformin** (Glucophage) + **Sulfonylurea** (Glipizide, Glyburide, Amaryl)
   - ☐ **Metformin** (Glucophage) + **Thiazolidinedione** (Pioglitazone, Actos)
   - ☐ **Metformin** (Glucophage) + **DPP-4 Inhibitor** (Januvia, Onglyza)
   - ☐ **Metformin** (Glucophage) + **GLP-1 Receptor Agonist** (Exentide, Liraglutide)
   - ☐ **Metformin** (Glucophage) + **Long-Acting Insulin** (Lantus, Glargine, Detemir, Levemir)

2. **How likely is the patient to adhere to your medication recommendations?** Mark only one.

   - ☐ Very likely to adhere
   - ☐ Somewhat likely to adhere
   - ☐ Somewhat unlikely to adhere
   - ☐ Very unlikely to adhere

Figure 1.2. Treatment Intensification for the Most and Least Complex Patient by Clinician Type

80-Year-Old, Cognitive Impairment, Heart Disease



65-Year-Old, No Cognitive Impairment, No Heart Disease

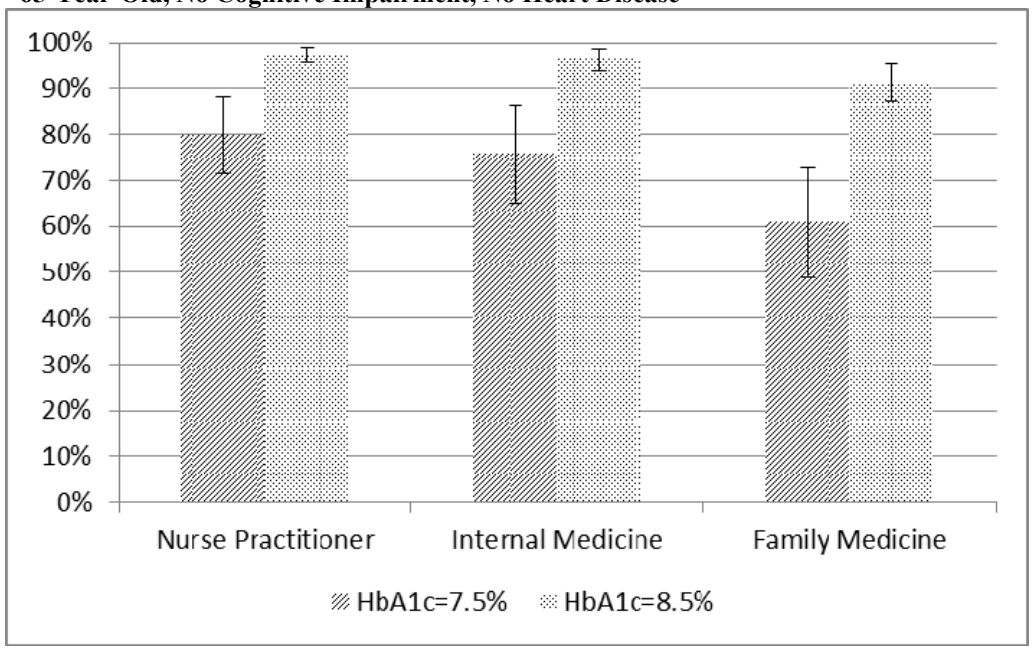


Figure 2.1 Sample Vignette

Mrs. Brown is **80 years old and has had type 2 diabetes for 15 years**. Three months ago, Mrs. Brown was prescribed Metformin 1000 mg (BID), an ACE inhibitor to control comorbid hypertension, and a low-dose aspirin. Mrs. Brown currently has a **HbA1c of 7.5%**, a BP of 140/80 mmHg, and a BMI of 29. Her basic metabolic profile is normal and GFR > 60. **Mrs. Brown has coronary artery disease, for which she underwent a coronary artery bypass graft five years ago**. Mrs. Brown reports an intermittent pain in her feet, but has difficulty localizing it. There is no history of depression. **Mrs. Brown has some recent memory loss on formal testing. She lives independently, but depends on her eldest daughter to keep her medical appointments and pay her bills. She stopped driving, in part because she occasionally got lost**. Mrs. Brown is able to afford her medications.

3. Which anti-hyperglycemic treatment option are you most likely to recommend? Mark only one.

- ☐ Continue **Metformin** (Glucophage) Monotherapy
- ☐ **Metformin** (Glucophage) + **Sulfonylurea** (Glipizide, Glyburide, Amaryl)
- ☐ **Metformin** (Glucophage) + **Thiazolidinedione** (Pioglitazone, Actos)
- ☐ **Metformin** (Glucophage) + **DPP-4 Inhibitor** (Januvia, Onglyza)
- ☐ **Metformin** (Glucophage) + **GLP-1 Receptor Agonist** (Exentide, Liraglutide)
- ☐ **Metformin** (Glucophage) + **Long-Acting Insulin** (Lantus, Glargine, Detemir, Levemir)

4. How likely is the patient to adhere to your medication recommendations? Mark only one.

- ☐ Very likely to adhere
- ☐ Somewhat likely to adhere
- ☐ Somewhat unlikely to adhere
- ☐ Very unlikely to adhere

Figure 2.2. Probability of Choosing Insulin or Sulfonylureas by Complexity and HbA1c Level

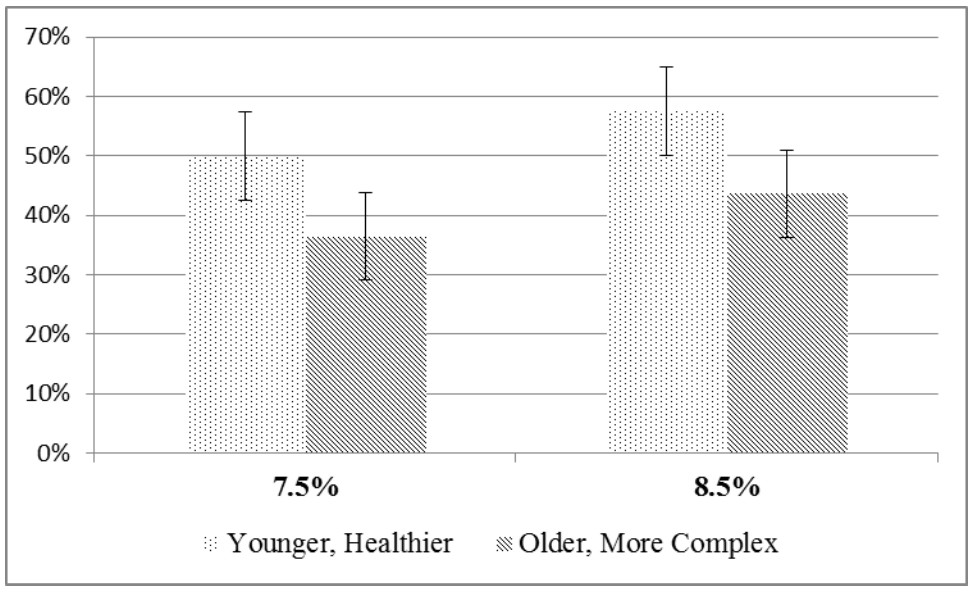
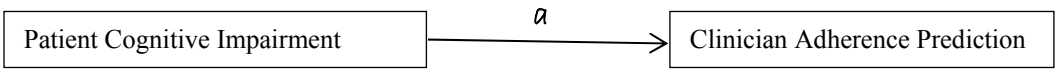
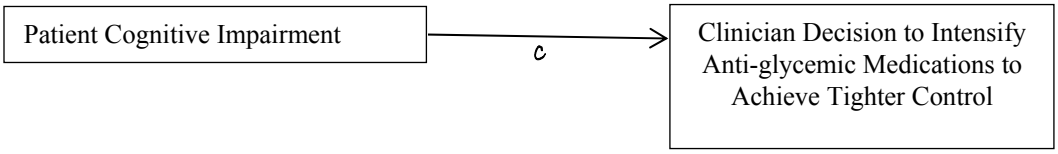


Figure 3.1. Partial Mediation Model Explored in the Current Vignette Study

A. Does patient cognitive impairment affect clinician adherence predictions?



B. Does patient cognitive impairment affect clinician antiglycemic treatment targets?



C. Do clinician adherence predictions partially explain, or mediate the relationship between patient cognitive impairment and antiglycemic treatment targets?

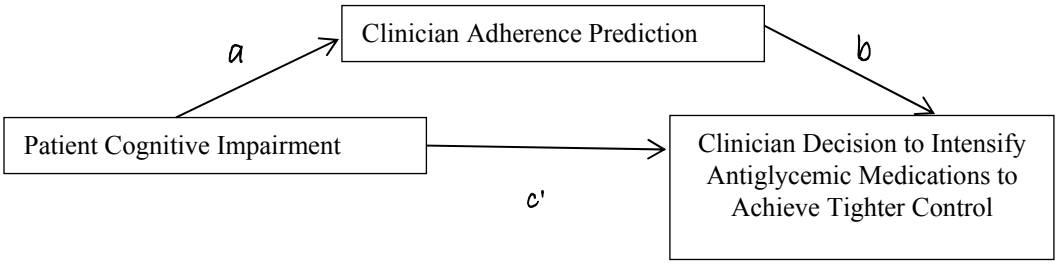


Figure 3.2. Sample Vignette

Mrs. Brown is **80 years old and has had type 2 diabetes for 15 years**. Three months ago, Mrs. Brown was prescribed Metformin 1000 mg (BID), an ACE inhibitor to control comorbid hypertension, and a low-dose aspirin. Mrs. Brown currently has a **HbA1c of 7.5%**, a BP of 140/80 mmHg, and a BMI of 29. Her basic metabolic profile is normal and GFR > 60. **Mrs. Brown has coronary artery disease, for which she underwent a coronary artery bypass graft five years ago**. Mrs. Brown reports an intermittent pain in her feet, but has difficulty localizing it. There is no history of depression. **Mrs. Brown has some recent memory loss on formal testing. She lives independently, but depends on her eldest daughter to keep her medical appointments and pay her bills. She stopped driving, in part because she occasionally got lost**. Mrs. Brown is able to afford her medications.

5. **Which anti-hyperglycemic treatment option are you most likely to recommend?** Mark only one.

   ☐ Continue **Metformin** (Glucophage) Monotherapy

   ☐ **Metformin** (Glucophage) + **Sulfonylurea** (Glipizide, Glyburide, Amaryl)

   ☐ **Metformin** (Glucophage) + **Thiazolidinedione** (Pioglitazone, Actos)

   ☐ **Metformin** (Glucophage) + **DPP-4 Inhibitor** (Januvia, Onglyza)

   ☐ **Metformin** (Glucophage) + **GLP-1 Receptor Agonist** (Exentide, Liraglutide)

   ☐ **Metformin** (Glucophage) + **Long-Acting Insulin** (Lantus, Glargine, Detemir, Levemir)

6. **How likely is the patient to adhere to your medication recommendations?** Mark only one.

   ☐ Very likely to adhere

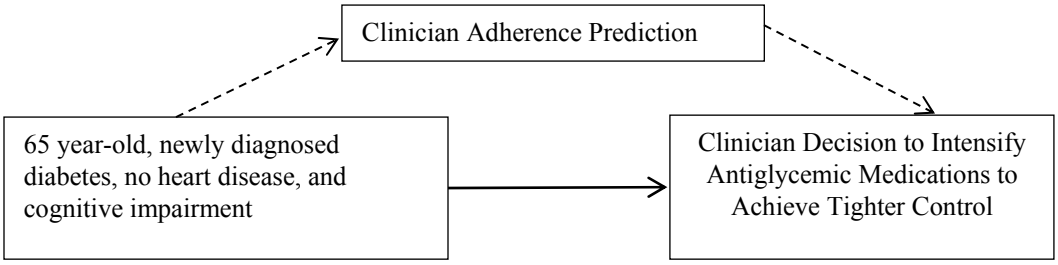
   ☐ Somewhat likely to adhere

   ☐ Somewhat unlikely to adhere

   ☐ Very unlikely to adhere

Figure 3.3. Predicted Adherence Affects Targets More for Older, More Complex Patients

A. Clinician adherence predictions less important in decision to intensify antihyperglycemic therapy for younger, otherwise healthy people with type 2 diabetes and evidence of cognitive impairment



B. Clinician adherence predictions more important in decision to intensify antihyperglycemic therapy for older, sicker people with type 2 diabetes and evidence of cognitive impairment

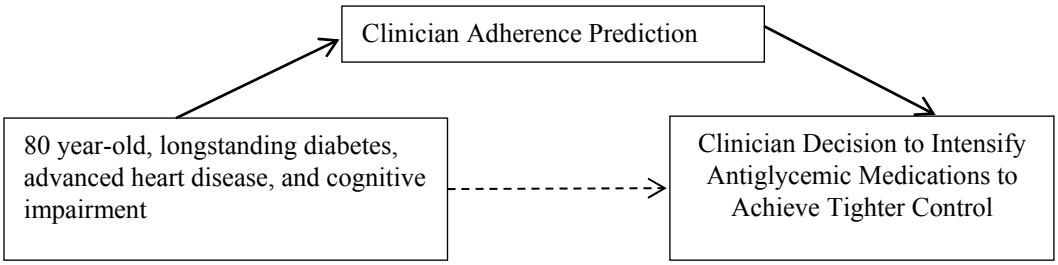


Table 1. Outcomes of Three Large Trials Comparing Intensive Glycemic Control to Standard Control among Patients with Established Type 2 Diabetes and Complications

	ACCORD (1999-2008)	ADVANCE (2001-2008	VADT (2000-2008)
Mean HbA1c - Intensive Control (I)	6.4%	6.50%	6.90%
Mean HbA1c - Standard Control (S)	7.5%	7.30%	8.40%
Mean Age ± SD	62±7	66±6	60±9
≥80 Years Old (%)	0.5	1.6	NR
All-Cause Mortality	I>S	NS	NS
Cardiovascular Mortality	I>S	NS	NS
Macrovascular Complications	I>S	NS	NS
Microvascular Complications	Albuminuria I<S Nephropathy/Retinopathy: NS	Major Microvascular Event (driven by nephropathy):I<S	Albuminuria I<S, Nephropathy/Neuropathy/Retinopathy:NS
Hypoglycemic Events	I>S	I>S	I>S

NR = Not Reported
NS = Not Significant
I>S = Outcome significantly higher in intensive treatment arm compared to standard treatment
I<S = Outcome significantly lower in intensive treatment arm compared to standard treatment

Table 2. ADA (2016) Guidelines for Older Adults with AGS (2013) Thresholds for Comparison

Patient Characteristics / Health Status	Rationale	Reasonable A1C goal‡	AGS (2013)
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	7%-7.5%
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	7.5%-8%
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	8%-9%

‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden.

*Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. By "multiple," we mean at least three, but many patients may have five or more.

**The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy.

†A1C of 8.5% (69 mmol/mol) equates to an estimated average glucose of 200 mg/dL (11.1 mmol/L). Looser A1C targets above 8.5% (69 mmol/mol) are not recommended as they may expose patients to more frequent higher glucose values and the acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing

Adapted from ADA (2016), Chapter 10., Table 10.1 (adapted), p.S83

Table 3. Dual Therapy Comparisons

	Metformin + **Sulfonylurea**	Metformin + **Thiazolidinedione**	Metformin + **DPP-4**	Metformin + **GLP-1**	Metformin + **Insulin**
Efficacy	High	High	Intermediate	High	High
Hypoglycemic Risk	Moderate Risk	Low Risk	Low Risk	Low Risk	Highest Risk
Weight	Gain	Gain	Neutral	Loss	Gain
Side Effects	Hypoglycemia	Edema, HF	Rare	GI	Hypoglycemic
Costs	Low	Low	High	High	Variable
*ADA (2016) Approaches to Glycemic Management, Figure 7.1, adapted					

Table 4. Vignette Factors and Levels

Vignette Factor	Level 1	Level 2
Glycated Hemoglobin (HbA1c)	HbA1c of 7.5%	HbA1c of 8.5%
Age/Disease Duration	65 years old / type 2 diabetes for 5 years	80 years old / type 2 diabetes for 15 years
Presence of Cognitive Impairment	[no information]	Some recent memory loss on formal testing She lives independently, but depends on her eldest daughter to keep her medical appointments and pay her bills She stopped driving, in part because she occasionally got lost
History of Heart Disease	no history of cardiovascular disease	coronary artery disease, for which she underwent a coronary artery bypass graft five years ago.

Table 1.1. ADA (2016) Guidelines for Older Adults with AGS (2013) Thresholds for Comparison

Patient Characteristics / Health Status	Rationale	Reasonable A1C goal‡	AGS (2013)
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	7%-7.5%
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	7.5%-8%
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	8%-9%

‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden.

*Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. By "multiple," we mean at least three, but many patients may have five or more.

**The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy.

†A1C of 8.5% (69 mmol/mol) equates to an estimated average glucose of 200 mg/dL (11.1 mmol/L). Looser A1C targets above 8.5% (69 mmol/mol) are not recommended as they may expose patients to more frequent higher glucose values and the acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing

Adapted from ADA (2016), Chapter 10., Table 10.1 (adapted), p.S83

Table 1.2. Vignette Factors and Levels

Vignette Factor	Level 1	Level 2
Glycated Hemoglobin (HbA1c)	HbA1c of 7.5%	HbA1c of 8.5%
Age/Disease Duration	65 years old / type 2 diabetes for 5 years	80 years old / type 2 diabetes for 15 years
Presence of Cognitive Impairment	[no information]	Some recent memory loss on formal testing She lives independently, but depends on her eldest daughter to keep her medical appointments and pay her bills She stopped driving, in part because she occasionally got lost
History of Heart Disease	no history of cardiovascular disease	coronary artery disease, for which she underwent a coronary artery bypass graft five years ago.

Table 1.3. Respondent Characteristics

	Total Sample (N=336)	**Family Practice (N=108)**	**Internal Medicine (N=73)**	**Nurse Practitioners (N=155)**
	Mean (Range)	Mean (Range)	Mean (Range)	Mean (Range)
Year Completed Professional Education	1996 (1955-2015)	1991 (1968-2015)	1986 (1955-2011)	2003 (1978-2015)
Length of Routine Visit (Minutes)	23 (5-90)	21 (7-45)	22 (5-90)	24 (5-60)
Medicare Patients as a Percent of Total Practice				
< 25%	28%	39%	16%	25%
25% - 75%	52%	50%	64%	48%
> 75%	20%	11%	19%	26%

Table 1.4. Rate of Anti-Hyperglycemic Treatment Intensification by Vignette Characteristics

	All Vignettes (n=1,344)		**HbA1c=7.5% (n=652)**		**HbA1c=8.5% (n=692)**	
	Percent Intensified (%)	Pearson χ^2	Percent Intensified (%)	Pearson χ^2	Percent Intensified (%)	Pearson χ^2
HbA1c						
7.50%	55.67	145.7**				
8.50%	85.55					
Age						
65-Year-Old	81.39	74.2**	70.43	64.7**	92.24	25.4**
80-Year-Old	60.06		39.09		78.78	
Heart Disease						
No Heart Disease	68.37	4.6*	53.99	0.80	82.25	5.8*
Heart Disease	73.68		57.36		88.70	
Cognitive Impairment						
No Cognitive Impairment	77.16	25.2**	60.56	6.1*	91.97	25.1**
Cognitive Impairment	64.75		50.91		78.55	

*p<.05, **p<.01

Table 1.5. Effect of Patient and Clinician Characteristics on Intensification

	Model 1. Patient Characteristics	**Model 2. Patient & Clinician Characteristics**	**Model 3. Patient-Level Interactions**	**Model 4. Clinician-Level Interactions**
	Percentage Points (SE)	Percentage Points (SE)	Percentage Points (SE)	Percentage Points (SE)
Patient Characteristics				
8.5% HbA1c	**31.7** **(.02)**	**31.7** **(.02)**	**31.5** **(.04)**	**31.1** **(.03)**
80-Year-Old	**-20.8** **(.02)**	**-20.9** **(.02)**	**-23.2** **(.03)**	**-20.8** **(.02)**
Heart Disease	3.0 (.02)	3.0 (.02)	-0.0 (.02)	3.5 (.02)
Cognitive Impairment	**-10.6** **(.02)**	**-10.6 (.02)**	**-5.9** **(.02)**	**-8.6** **(.02)**
Clinician Characteristics				
Clinician Type (ref. Nurse Practitioner)				
General Internist		-2.2 (.04)	-3.9 (.04)	-3.8 (.04)
Family Practice		**-14.6** **(.04)**	**-16.3** **(.04)**	-13.1 (.05)
Length of Routine Visit > 20 Minutes		-.8 (.03)		
>75% of Practice is Medicare Patients		-1.0 (.04)		
Completed Education in Last 5 Years		6.0 (.03)		
HbA1c Interactions with Patient Factors				
HbA1c 8.5%*80-Year-Old			4.9 (.04)	
HbA1c 8.5%*Heart Disease			7.2 (.04)	
HbA1c 8.5%*Cognitive Impairment			**-11.7** **(.04)**	
Family Medicine Interactions				
Family Medicine*HbA1c 8.5%				1.5 (.04)
Family Medicine*80-Year-Old				1.5 (.04)
Family Medicine*Heart Disease				-.9 (.04)
Family Medicine*Cognitive Impairment				-5.4 (.04)
Model Intraclass Correlation	0.63	0.60	0.63	0.61

***p<.05, **p<.01**

Table 2.1. Dual Therapy Comparisons

	Metformin + **Sulfonylurea**	Metformin + **Thiazolidinedione**	Metformin + **DPP-4**	Metformin + **GLP-1**	Metformin + **Insulin**
Efficacy	High	High	Intermediate	High	High
Hypoglycemic Risk	Moderate Risk	Low Risk	Low Risk	Low Risk	Highest Risk
Weight	Gain	Gain	Neutral	Loss	Gain
Side Effects	Hypoglycemia	Edema, HF	Rare	GI	Hypoglycemic
Costs	Low	Low	High	High	Variable
*ADA (2016) Approaches to Glycemic Management, Figure 7.1, adapted					

Table 2.2. Vignette Factors and Levels

Vignette Factor	Level 1	Level 2
Glycated Hemoglobin (HbA1c)	HbA1c of 7.5%	HbA1c of 8.5%
Age/Disease Duration	65 years old / type 2 diabetes for 5 years	80 years old / type 2 diabetes for 15 years
Presence of Cognitive Impairment	[no information]	Some recent memory loss on formal testing She lives independently, but depends on her eldest daughter to keep her medical appointments and pay her bills She stopped driving, in part because she occasionally got lost
History of Heart Disease	no history of cardiovascular disease	coronary artery disease, for which she underwent a coronary artery bypass graft five years ago.

Table 2.3. Respondent Characteristics

	Total Sample (N=336)	**Family Practice (N=108)**	**Internal Medicine (N=73)**	**Nurse Practitioners (N=155)**
	Mean (Range)	Mean (Range)	Mean (Range)	Mean (Range)
Year Completed Professional Education	1996 (1955-2015)	1991 (1968-2015)	1986 (1955-2011)	2003 (1978-2015)
Length of Routine Visit (Minutes)	23 (5-90)	21 (7-45)	22 (5-90)	24 (5-60)
Medicare Patients as a Percent of Total Practice				
< 25%	28%	39%	16%	25%
25% - 75%	52%	50%	64%	48%
> 75%	20%	11%	19%	26%

Table 2.4. Bivariate Relationship between Vignette Factors and Second-Line Medication Choice

	Sulfonylurea (34%)	**Insulin (13%)**	**TZD (7%)**	**GLP-1 (10%)**	**DPP-4 (35%)**	
	%	%	%	%	%	χ^2
HbA1c						
7.5%	34.7	7.7	8.0	9.6	39.9	**17.3****
8.5%	33.9	16.3	6.4	10.9	32.5	
Age						
65-Year-Old	35.6	13.5	6.2	11.5	33.2	6.0
80-Year-Old	32.1	12.3	8.2	8.7	38.6	
Heart Disease						
No Heart Disease	33.9	11.0	8.4	9.9	36.8	5.6
Heart Disease	34.5	14.8	5.8	10.8	34.1	
Cognitive Impairment*						
No Cognitive Impairment	34.6	16.5	5.5	12.4	31.0	**25.9****
Cognitive Impairment	33.7	8.7	8.9	8.0	40.8	

***p<.05, **p<.01**

TZD = Thiazolidinedione, GLP-1 = GLP-1 Receptor Agonist, DPP-4 = DPP-4 Inhibitor

Table 2.5. Effect of Vignette and Clinician Factors on Second-Line Anti-Hyperglycemic Medication Choice

	Sulfonylurea	**Insulin**	**TZD**	**GLP**	**DPP4**
	Percentage Points (SE)	Percentage Points (SE)	Percentage Points (SE)	Percentage Points (SE)	Percentage Points (SE)
Patient Characteristics					
8.5% HbA1c	1.2 (.03)	**6.3* (.03)**	-0.8 (.02)	0.5 (.02)	**-7.2* (.03)**
80-Year-Old	-3.9 (.03)	-1.6 (.03)	0.7 (.02)	-3.8 (.02)	**8.6* (.01)**
Heart Disease	0.4 (.03)	2.4 (.02)	-2.6 (.02)	1.0 (.02)	-1.3 (.03)
Cognitive Impairment	0.5 (.03)	**-7.3** (.02)**	**3.5* (.01)**	**-4.5* (.02)**	**7.8* (.03)**
Clinician Characteristics					
Clinician Type (ref. Nurse Practitioner)					
Internal Medicine	**16.3* (.07)**	-3.2 (.05)	-2.5 (.03)	-4.4 (.05)	-6.2 (.07)
Family Practice	11.0 (.06)	-4.4 (.04)	0.5 (.03)	-1.7 (.04)	-5.4 (.06)
Length of Routine Visit > 20 Minutes	-4.9 (.05)	.2 (.03)	-.6 (.03)	.5 (.03)	4.8 (.05)
>75% of Practice is Medicare Patients	-.1.8 (.05)	**12.2* (.04)**	-2.7 (.02)	-3.2 (.03)	-4.6 (.05)
Completed Education in Last 5 Years	7.4 (.05)	-4.5 (.03)	3.0 (.03)	3.5 (.03)	-9.5 (.05)

***p<.05**

TZD = Thiazolidinedione, GLP-1 = GLP-1 Receptor Agonist, DPP-4 = DPP-4 Inhibitor

Table 3.1. Vignette Factors and Levels

Vignette Factor	Level 1	Level 2
Glycated Hemoglobin (HbA1c)	HbA1c of 7.5%	HbA1c of 8.5%
Age/Disease Duration	65 years old / type 2 diabetes for 5 years	80 years old / type 2 diabetes for 15 years
Presence of Cognitive Impairment	[no information]	Some recent memory loss on formal testing She lives independently, but depends on her eldest daughter to keep her medical appointments and pay her bills She stopped driving, in part because she occasionally got lost
History of Heart Disease	no history of cardiovascular disease	coronary artery disease, for which she underwent a coronary artery bypass graft five years ago.

Table 3.2. Respondent Characteristics

	Total Sample (N=336)	**Family Practice (N=108)**	**Internal Medicine (N=73)**	**Nurse Practitioners (N=155)**
	Mean (Range)	Mean (Range)	Mean (Range)	Mean (Range)
Year Completed Professional Education	1996 (1955-2015)	1991 (1968-2015)	1986 (1955-2011)	2003 (1978-2015)
Length of Routine Visit (Minutes)	23 (5-90)	21 (7-45)	22 (5-90)	24 (5-60)
Medicare Patients as a Percent of Total Practice				
< 25%	28%	39%	16%	25%
25% - 75%	52%	50%	64%	48%
> 75%	20%	11%	19%	26%

Table 3.3. Relationship between Patient Vignette Characteristics and Clinician Predicted Adherence

	Age		Cognitive Impairment (CI)		Heart Disease (HD)		Glycated Hemoglobin (HbA1c)	
	65	80	No CI	CI	No HD	HD	7.5%	8.5%
Unlikely to Adhere	11.4%	12.4%	3.1%	21.0%	12.1%	11.8%	11.7%	12.1%
Likely To Adhere	88.6%	87.6%	96.9%	79.0%	88.0%	88.2%	88.3%	87.90%
Pearson $\chi 2$	0.35		103.3**		0.03		0.07	

***p<.05, **p<.01**

Table 3.4. Relationship between Patient Vignette Characteristics and a Clinician's Decision to Intensify Medication Therapy

	Age		Cognitive Impairment (CI)		Heart Disease (HD)		Glycated Haemoglobin (HbA1c)	
	65	80	No CI	CI	No HD	HD	7.5%	8.5%
No Intensify	18.6%	39.9%	22.8%	35.3%	31.6%	26.3%	44.3%	14.5%
Intensify	81.4%	60.1%	77.2%	64.8%	68.4%	73.7%	55.7%	85.60%
Pearson $\chi 2$	74.2**		25.2**		4.6*		145.7**	

***p<.05, **p<.01**

Table 3.5. Mediation Relationships from Mixed Effects Probit Regressions

Relationship being Tested	**X→Y**	**X→M**	**M→Y (when X present)**
Key Finding	1. Cognitive Impairment Negatively Related to Treatment Intensification	2. Cognitive Impairment Negatively Related to Predicted Adherence	3. Predicted adherence not significantly related to treatment intensification
	Percentage Points (SE)	Percentage Points (SE)	Percentage Points (SE)
Patient Characteristics			
Cognitive Impairment	-10.6** (.02)	-18.7** (.02)	-10.0** (.02)
8.5% HbA1c	31.7** (.02)	-1.5 (.01)	31.8** (.02)
80-Year-Old	20.9** (.02)	-.9 (.01)	-20.9** (.02)
Heart Disease	3.0 (.02)	0.1 (.01)	3.0 (.02)
Provider Characteristics			
Practitioner Type (ref. Nurse Practitioner)			
General Internist	-2.2 (.04)	-5.2 (.03)	-2.0 (.04)
Family Practice	-14.5** (.04)	-1.7 (.03)	-14.5** (.04)
Length of Routine Visit > 20 Minutes	-.8 (.03)	-5.5* (.02)	-.6 (.03)
>75% of Practice is Medicare Patients	-1.0 (.04)	3.9 (.03)	-1.2 (.04)
Completed Education in Last 5 Years	6.0 (.03)	.9 (.03)	6.1 (.03)
Clincian Predicts Patient will be Adherent			3.0 (.03)

***p<.05, **p<.01**

Table 5. Summary of Findings for Papers 1 and 2.

Factor	Comparator	Medication Intensification	Choose Sulfonylurea or Insulin
HbA1c of 8.5%	7.5%	+ 32%	+ 8%
80, Long Disease Duration	65, Short Disease Duration	- 21%	- 6%
Cognitive Impairment	No information	- 11%	- 10%
Heart Disease requiring CABG	No history of heart disease	NS	NS
Family Medicine	Nurse Practitioner	- 16%	NS
Over 75% of practice Medicare	≤75% Medicare	NS	+ 11%
Most Complex, HbA1c 7.5% (predicted probability)	NA	35%	36%
Least Complex, HbA1c 7.5% (predicted probability)	NA	75%	50%

18 Appendices

Appendix A. Sample Consent Form and Survey

CONSENT STATEMENT

Diabetic Anti-Hyperglycemic Medication Survey

You are invited to complete a survey on diabetic anti-hyperglycemic medications. Please read this form and ask any questions you may have before agreeing to complete the survey. This study is being conducted as part of a dissertation requirement for the University of Minnesota, Health Services Research, Policy and Administration Program.

Background Information

This project seeks to understand how primary care physicians choose between available anti-hyperglycemic medications and predict adherence. The results of this survey will provide information to researchers and educators.

Procedures

If you agree to participate, you will be asked to complete a short survey in which you will be given four short clinical scenarios and asked to recommend a course of treatment. The survey should take about 4 minutes.

Risks and Benefits of Being in the Study

There are no immediate or expected risks for participating in the survey. You are simply helping us understand how physicians treat diabetic patients. The survey is completely anonymous.

There are also no immediate or expected benefits to you for participating in the survey.

Voluntary Nature of the Study

If you decide to participate, you are free to withdraw at any time.

Contacts and Questions

The researcher conducting this study is Ellen McCreedy. You may ask any questions you have now. If you have questions later, you may contact her at 813-731-4241. If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher, contact Research Subjects' Advocate line, D528 Mayo, 420 Delaware Street S.E., Minneapolis, Minnesota 55455; telephone (612) 625-1650.

You may have a copy of this form to keep for your records.

Diabetic Anti-Hyperglycemic Medication Survey

Thank you for helping with this survey. We appreciate you sharing your time and expertise. Please note that your responses are anonymous. This survey takes approximately 4 minutes to complete. Feel free to add any additional comments at the end of the survey.

Part I. Patient Vignettes

Instructions: For each of the following hypothetical type 2 diabetics, please determine the appropriate anti-hyperglycemic medication treatment option and the extent to which the patient is likely to be adherent to this treatment. Please try to make a decision with the information provided in the vignettes.

Vignette 1. Mrs. Williams is **65 years old and has had type 2 diabetes for 5 years**. Three months ago, Mrs. Williams was prescribed Metformin 1000 mg (BID), an ACE inhibitor to control comorbid hypertension, and a low-dose aspirin. Mrs. Williams currently has a **HbA1c of 8.5%**, a BP of 140/80 mmHg, and a BMI of 29. Her basic metabolic profile is normal and GFR > 60. **Mrs. Williams has coronary artery disease, for which she underwent a coronary artery bypass graft five years ago**. Mrs. Williams reports an intermittent pain in her feet, but has difficulty localizing it. There is no history depression. Mrs. Williams is able to afford her medications.

1. Which anti-hyperglycemic treatment option are you most likely to recommend? Mark only one.

- ☐ Continue **Metformin** (Glucophage) Monotherapy, **Same Dose**
- ☐ Continue **Metformin** (Glucophage) Monotherapy, **Increase Dose**
- ☐ **Metformin** (Glucophage) + **Sulfonylurea** (Glipizide, Glyburide, Amaryl)
- ☐ **Metformin** (Glucophage) + **Thiazolidinedione** (Pioglitazone, Actos)
- ☐ **Metformin** (Glucophage) + **DPP-4 Inhibitor** (Januvia, Onglyza)
- ☐ **Metformin** (Glucophage) + **GLP-1 Receptor Agonist** (Exentide, Liraglutide)
- ☐ **Metformin** (Glucophage) + **Long-Acting Insulin** (Lantus, Glargine, Detemir, Levemir)

2. How likely is the patient to adhere to your medication recommendations? Mark only one.

- ☐ Very likely to adhere
- ☐ Somewhat likely to adhere
- ☐ Somewhat unlikely to adhere
- ☐ Very unlikely to adhere

Vignette 2. Mrs. Johnson is **80 years old and has had type 2 diabetes for 15 years**. Three months ago, Mrs. Johnson was prescribed Metformin 1000 mg (BID), an ACE inhibitor to control comorbid hypertension, and a low-dose aspirin. Mrs. Johnson currently has a **HbA1c of 7.5%**, a BP of 140/80 mmHg, and a BMI of 29. Her basic metabolic profile is normal and GFR > 60. Mrs. Johnson reports an intermittent pain in her feet, but has difficulty localizing it. There is no history of cardiovascular disease or depression. Mrs. Johnson is able to afford her medications.

1. Which anti-hyperglycemic treatment option are you most likely to recommend? Mark only one.

- ☐ Continue **Metformin** (Glucophage) Monotherapy, **Same Dose**
- ☐ Continue **Metformin** (Glucophage) Monotherapy, **Increase Dose**
- ☐ **Metformin** (Glucophage) + **Sulfonylurea** (Glipizide, Glyburide, Amaryl)
- ☐ **Metformin** (Glucophage) + **Thiazolidinedione** (Pioglitazone, Actos)
- ☐ **Metformin** (Glucophage) + **DPP-4 Inhibitor** (Januvia, Onglyza)
- ☐ **Metformin** (Glucophage) + **GLP-1 Receptor Agonist** (Exentide, Liraglutide)
- ☐ **Metformin** (Glucophage) + **Long-Acting Insulin** (Lantus, Glargine, Detemir, Levemir)

2. How likely is the patient to adhere to your medication recommendations? Mark only one.

- ☐ Very likely to adhere
- ☐ Somewhat likely to adhere
- ☐ Somewhat unlikely to adhere
- ☐ Very unlikely to adhere

Vignette 3. Mrs. Jones is **65 years old and has had type 2 diabetes for 5 years**. Three months ago, Mrs. Jones was prescribed Metformin 850 mg (BID), an ACE inhibitor to control comorbid hypertension, and a low-dose aspirin. Mrs. Jones currently has a **HbA1c of 7.5%**, a BP of 140/80 mmHg, and a BMI of 29. Her basic metabolic profile is normal and GFR > 60. Mrs. Jones reports an intermittent pain in her feet, but has difficulty localizing it. There is no history of cardiovascular disease or depression. **Mrs. Jones has some recent memory loss on formal testing. She lives independently, but depends on her eldest daughter to keep her medical appointments and pay her bills. She stopped driving, in part because she occasionally got lost**. Mrs. Jones is able to afford her medications.

1. Which anti-hyperglycemic treatment option are you most likely to recommend? Mark only one.

- ☐ Continue **Metformin** (Glucophage) Monotherapy, **Same Dose**
- ☐ Continue **Metformin** (Glucophage) Monotherapy, **Increase Dose**
- ☐ **Metformin** (Glucophage) + **Sulfonylurea** (Glipizide, Glyburide, Amaryl)
- ☐ **Metformin** (Glucophage) + **Thiazolidinedione** (Pioglitazone, Actos)
- ☐ **Metformin** (Glucophage) + **DPP-4 Inhibitor** (Januvia, Onglyza)
- ☐ **Metformin** (Glucophage) + **GLP-1 Receptor Agonist** (Exentide, Liraglutide)
- ☐ **Metformin** (Glucophage) + **Long-Acting Insulin** (Lantus, Glargine, Detemir, Levemir)

2. How likely is the patient to adhere to your medication recommendations? Mark only one.

- ☐ Very likely to adhere
- ☐ Somewhat likely to adhere
- ☐ Somewhat unlikely to adhere
- ☐ Very unlikely to adhere

Vignette 4. Mrs. Brown is **65 years old and has had type 2 diabetes for 5 years**. Three months ago, Mrs. Brown was prescribed Metformin 850 mg (BID), an ACE inhibitor to control comorbid hypertension, and a low-dose aspirin. Mrs. Brown currently has a **HbA1c of 8.5%**, a BP of 140/80 mmHg, and a BMI of 29. Her basic metabolic profile is normal and GFR > 60. Mrs. Brown reports an intermittent pain in her feet, but has difficulty localizing it. There is no history of cardiovascular disease or depression. **Mrs. Brown has some recent memory loss on formal testing. She lives independently and seems to be able to function on her own with only minimal assistance. However, she stopped driving, in part because she occasionally got lost, and she no longer manages her personal finances.**

1. Which anti-hyperglycemic treatment option are you most likely to recommend? Mark only one.

- ☐ Continue **Metformin** (Glucophage) Monotherapy, **Same Dose**
- ☐ Continue **Metformin** (Glucophage) Monotherapy, **Increase Dose**
- ☐ **Metformin** (Glucophage) + **Sulfonylurea** (Glipizide, Glyburide, Amaryl)
- ☐ **Metformin** (Glucophage) + **Thiazolidinedione** (Pioglitazone, Actos)
- ☐ **Metformin** (Glucophage) + **DPP-4 Inhibitor** (Januvia, Onglyza)
- ☐ **Metformin** (Glucophage) + **GLP-1 Receptor Agonist** (Exentide, Liraglutide)
- ☐ **Metformin** (Glucophage) + **Long-Acting Insulin** (Lantus, Glargine, Detemir, Levemir)

2. How likely is the patient to adhere to your medication recommendations? Mark only one.

- ☐ Very likely to adhere
- ☐ Somewhat likely to adhere
- ☐ Somewhat unlikely to adhere
- ☐ Very unlikely to adhere

Part II. Professional Background

Instructions: Please provide some information about your professional background and practice.

1. What year did you finish your professional education (medical school for physicians)?
(Year)

2. What type of clinician are you?

- ☐ Family Medicine Physician
- ☐ Internal Medicine Physician
- ☐ Nurse Practitioner
- ☐ Other, Specify:

3. What is the average length of a routine visit in your practice? _____Minutes

4. Approximately what percent of your practice is Medicare?

- ☐ < 25%
- ☐ 25% - 75%
- ☐ > 75%

We care about your input. Please use the back of this page to make any final comments about how anti-hyperglycemic medication and adherence determinations are made in practice.

Thank you!

Appendix B. Sample Approach Email for Leaders of Practice-Based Research Networks

Dr. XX,

The rate of hospitalizations for hypoglycemia now exceeds that for hyperglycemia among older diabetics. Accepting higher HbA1c levels for older adults with longstanding disease, cognitive impairment and multiple comorbidities is the recommendation of the American Geriatrics Society and a priority of the Choosing Wisely initiative. Yet, overtreatment is still widespread.

The following scenario study will help your Practice-Based Research Network (PBRN) understand how physicians perform to nationally established guidelines and could serve a launching point for continuing education around the treatment of older adults with diabetes. We are hoping to enroll 250 primary care physicians in this project.

The online questionnaire, sponsored and approved by the University of Minnesota, takes less than 5 minutes to complete and can be distributed to membership via a common link. Participating PBRNs will receive a summary of their results and a comparison of their results to de-identified responses from other PBRNs for benchmarking purposes. Responses are anonymous. Specific physicians will not be identified to anyone.

A one-page summary of the project and a sample questionnaire are attached to this email. Please feel free to contact me with any questions. We look forward to hearing from you. Thank you.

Best,

Ellen McCreedy

PI: Ellen McCreedy
Doctoral Candidate
Health Policy and Management
U of MN School of Public Health
420 Delaware St SE (MMC 729)
Minneapolis, MN 55455
(813) 731-4241
mccr0184@umn.edu

Sponsor: Robert Kane, MD
Professor and Minnesota Chair in Long-Term Care and Aging
Health Policy and Management
U of MN School of Public Health
420 Delaware St SE (MMC 729)
Minneapolis, MN 55455

Appendix C. Sample Recruitment Email with Embedded Link to Survey

We are inviting you to participate in a survey on diabetic anti-hyperglycemic medication choices for older people. This study is being conducted by the University of Minnesota with no external funding from any pharmaceutical manufacturer. We are trying to assess the range of approaches clincians use in providing care for their patients with diabetes. The survey takes about 4 minutes to complete and responses are anonymous.

https://umn.qualtrics.com/SE/?SID=SV_9uEVQQkHqodo5pP

For more information, contact:

Ellen McCreedy, PI
Doctoral Candidate
Health Policy and Management
U of MN School of Public Health
420 Delaware St SE (MMC 729)
Minneapolis, MN 55455
mccr0184@umn.edu

Robert Kane, MD, Sponsor
Professor and Minnesota Chair in Long-Term Care and Aging
Health Policy and Management
U of MN School of Public Health
420 Delaware St SE (MMC 729)
Minneapolis, MN 55455

Thank you for your time and interest in supporting primary care.